COMPARATIVE EFFICACY OF INTRA LESIONAL TRIAMCINOLONE ACETONIDE AND 5-FLUOROURACIL FOR KELOIDS

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BY

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Dedicated to

my

Family

&

Teachers

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Dr. Amandeep Kaur

ABBREVIATIONS

TAC	Triamcinolone Acetonide
5-FU	5-Fluorouracil
VSS	Vancouver Scar Scale
VAS	Visual Analogue Score
PSS	Patient Satisfaction Score
ECM	Extra Cellular Matrix
TGF	Transforming Growth Matrix
PDL	Pulsed Dye Laser

ABSTRACT

Introduction: A keloid is an overgrowth of dense and fibrous tissue usually developing after healing of skin injury. There are various non-surgical and surgical modalities for the treatment of the keloids. Intra lesional Triamcinolone acetonide (TAC) and 5-Fluorouracil (5-FU) are most commonly used these days for keloids. We performed a comparative study between intra lesional Triamcinolone acetonide and 5-Fluorouracil to assess their efficacy in the treatment of keloids.

Materials and Methods: This study was conducted in the Department of Plastic and Reconstructive Surgery of DMCH, Ludhiana included 40 patients, divided into two groups, (Group A and Group B) with 20 patients each, according to the computer generated randomization list

Group A patients received intra lesional TAC (40 mg/ml) in the dose of 4 mg/cm^2 or 0.1 ml/cm^2 at 3 weeks interval using insulin syringe.

Group B patients received intra lesional 5-FU (50 mg/ml) in the dose of 10 mg/cm^2 or 0.2 ml/cm^2 at 3 weeks interval using insulin syringe. Assessment of the scar was done using three parameters i.e., Vancouver Scar Scale, Visual Analogue Scale and Patient Satisfaction Score. Assessment was done at 3 weekly intervals till the 5th visit or till the scar settled (whichever was earlier). Mean of all the visits was taken for assessing the final outcome.

Results: Patients receiving TAC had a lower Visual Analogue Score than those receiving 5-FU (2.085 vs 3.18). Reduction in the Vancouver Scar Scale was seen in both treatment arms. However, 5-FU produced a more marked reduction in the Vancouver Scar Scale than TAC (2.57 vs 2.68). Patient Satisfaction Score was higher in TAC group than 5-FU group (1.97 vs 1.78).

Conclusion: This study concluded that 5-FU elicits a better response than TAC in terms of pliability, height, pigmentation and vascularity of keloid scars. 5-FU results in better resolution of keloids. 5-FU is less well tolerated and is associated with more side effects especially ulceration at

injection site. Patient satisfaction score is better with TAC though the keloid resolution and pain reduction are better with 5-FU.

Key words: Keloids, Intra lesional therapy, Triamcinolone acetonide, 5-Fluorouracil.

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INTRODUCTION

The word scar is derived from the Greek word *eskhara*, which means scab. Scar is a lingering sign of damage or injury to skin. Scarring is an inevitable mark following healing of a wound or burn. Any wound that penetrates deeper than the epidermis, inflicted by biologic, chemical, or physical injury, results in healing by scar formation.[1]

There is a spectrum of scar formation, with scar less regeneration on one end, ‘‘normal’’ scar formation in the center, and pathological scar formation, including hypertrophic and keloid scarring, on the other end. Keloid and hypertrophic scarring contribute to much of the morbidity of scarring after surgery.

Keloid scars, represent an abnormally exuberant scarring response that extends beyond the borders of the original injury. Keloids continue to evolve over time, without a quiescent or regressive phase and do infiltrate the surrounding tissue. Keloids appear as firm, mildly tender, bosselated tumors with a shiny surface and occasional telangiectasia. The epithelium is thinned and there may be focal areas of ulceration. The color is pink to purple and may be accompanied by hyper pigmentation.[2] The initial lesions are erythematous and become brownish red, followed by paling as they age. The lesions preferentially develop on the ear lobes, shoulders and pre sternal skin; which are void of hair follicles and other glands.

Histological features of keloid that distinguish it from normal skin and hypertrophic scar include whorls and nodules of thick, hyalinized collagen bundles, known as keloidal collagen, and tongue like projections of scar tissue that advance underneath the surrounding normal epidermis.[3] Compared with hypertrophic scar, keloid scar has relatively non-flattened overlying epidermis and non-fibrotic papillary dermis.[4]

Keloids occur when the delicate balance of the deposition and degradation of Extra Cellular Matrix (ECM) proteins is disrupted. This happens due to either excessive production of the collagen, proteoglycans and fibronectin by fibroblasts or due to deficient

degradation and remodeling of the ECM. The keloids can be painful, pruritic, erythematous, raised and cosmetically unacceptable.

Multiple studies on keloid formation have led to a multitude of therapeutic strategies to prevent or improve keloid formation and have been reviewed in a plethora of articles. However, only a few of them have been supported by well-designed prospective studies with adequate control groups.[5]

Currently, a wide variety of different keloid scar management measures have been advocated both to prevent and to treat unaesthetic or excessive scar formation.

Management of keloids has evolved from the non invasive therapies like application of silicon gel sheets, pressure therapy to minimally invasive procedures like laser therapy, cryotherapy, radiation therapy to intralesional injections of steroids and 5-Fluorouracil to invasive procedures like surgical excision with or without grafting.

The very fact that so many treatment options have been mentioned in the literature suggest that none of the therapeutic measures is fully effective in keloid management.

Intralesional steroid injections have been used for the therapy of excessive scars since the mid-1960s.[6] To date, the use of Intralesional Triamcinolone acetonide represents the therapy of choice for keloids and effectively provides symptomatic relief by reducing pruritis.[7] Effects of the corticosteroids result primarily from their suppressive effects on the inflammatory process in the wound, and secondarily from reduced collagen and glycosaminoglycan synthesis, inhibition of fibroblast growth, as well as enhanced collagen and fibroblast degeneration.[8-10] Intralesional corticosteroid injections improve scar pliability, diminish its volume and height and reduce scar related itching and pain. The most used current protocol involves insoluble Triamcinolone acetonide (10-40 mg/ml), alone or better in combination with lidocaine, weekly, biweekly or monthly.[11] Complications such as hypo pigmentation, skin atrophy, telangiectasias, rebound effects, ineffectiveness and injection pain have been noted with the therapy.

Triamcinolone acetonide is a proven therapy for the management of keloids.

Another drug that has generated response in keloid scars is an anti-neoplastic agent 5-Fluorouracil (5-FU). The response is attributed to the fact that keloids exist in a hyper metabolic state.[12] 5-Fluorouracil is a fluorinated pyrimidine analog that acts as an anti-metabolic agent, inhibiting thymidylate synthesis and interfering with RNA synthesis. The anti-metabolite 5-Fluorouracil has been shown to inhibit fibroblast proliferation in a dose dependent manner, and with increasing dosages 5-FU induced cell cycle arrests at the G2/ M phase with eventual cell apoptosis.[13]

However, there is a lack of sufficient clinical trials with a large number of patients to assess efficacy, safety profile and recurrence rates when using 5-FU as an immunotherapy for the treatment of keloid scars.

5-Fluorouracil has a comparatively faster response in scar flattening. Both in vitro and in vivo studies have confirmed that 5-Fluorouracil inhibits collagen synthesis.[4,12-15]

Intralesional Triamcinolone acetonide and 5-Fluorouracil are proven therapies for the management of keloids but the comparative efficacy of these two have not been studied much. Progress in the identification of effective treatment regimens through clinical research has been hampered by the lack of a universally accepted methods of measuring outcome.

The Vancouver Scar Scale, first described by Sullivan et al. in 1990 has become one of the most widely applied scar assessment scales in clinical research.[16, 17] Although originally designed for burns, the Vancouver Scar Scale has been found to be clinically useful in evaluating a wide range of scar types and has become established in many units across the world as the standard mode of assessment. It allows assessment of pigmentation, vascularity, pliability, and scar height. Each of these variables is relevant to keloid scars which, without treatment, are typically pigmented, vascular (especially apparent in patients with light skin tones), stiff, and raised.

Pain is another bothersome symptom secondary to keloids. In order to objectively assess and compare regression of pain in such patients, we have used Visual Analogue Scale (VAS).

Quinn et al. in their study in 1995 assessed the cosmetic outcomes of scars after skin injury treatment using the VAS. They considered that conventional scales assess pain and cosmetic factors in a subjective manner; therefore, the scale needs to be able to objectively assess scars.[18]

Another parameter which can subjectively assess the satisfaction of the patient with regards to response to the treatment is Patient Satisfaction Score. We have added this parameter in this study. This score is an essential part of health care quality assessment.[19]

In this study we will compare the efficacy of the intralesional Triamcinolone acetonide and 5-Fluorouracil for keloids by Vancouver Scar Scale, Visual analogue scale (for pain) and Patient Satisfaction Score.

AIMS AND OBJECTIVES

To compare the efficacy of intralesional Triamcinolone acetonide (TAC) and 5-Fluorouracil (5-FU) for keloids.

REVIEW OF LITERATURE

A keloid is an overgrowth of dense, fibrous tissue, usually developing after healing of skin injury.[2] This tissue extends beyond the borders of the original wound, does not regress spontaneously and tends to recur after excision.

Keloids are benign proliferative growths of dermal collagen that usually result from an excessive tissue response to skin trauma in predisposed individual.[20] There are, however, spontaneous keloids that arise without a history of trauma to involved site, specially keloids on the mid chest area. Keloids grow beyond the boundaries of the original wound, in contradiction to hypertrophic scars, which remain within those boundaries. Keloids, therefore are thick scar tissues of human skin which have escaped the boundaries of the original wound to invade the surrounding normal skin and produced by deposition of excessive amounts of collagen tissue over prolonged periods.

Various treatment and preventive options for keloids are:

1. Massage

Massage, manual or mechanical (i.e., compressed air, threadlike shower, etc.), is standard therapy in rehabilitation centers specializing in the treatment of keloids.[21, 22]

2. Pressure garments

Mechanical compression is shown to reduce collagen synthesis by several mechanisms. These include decreased blood, oxygen and nutrient delivery to the scar. It has been reported that pressure garments should be worn at least 23 hours a day, at 20–40 mm Hg (better around the low range), starting as soon as possible after wound re-epithelialization, for 6–24 months.[23] Pressures below 10 mm Hg have been shown to produce no beneficial effects, whereas pressures exceeding 40 mm Hg may lead to paresthesias and skin maceration.

3. Silicone gel sheeting

Hydration and occlusion have been suggested to be the main mechanisms of action of topical adhesive tape (plastic or paper) and silicone materials (sheets, strips, gels, creams, sprays and foams;

available over the counter or custom-made).[24] Silicone sheets are recommended to be worn for 12–24 hours a day for at least 2 months, beginning 2 weeks after wound healing.

4. Laser and light-based therapy

The conventional short-pulsed dye laser (585 nm PDL) has been described as the most appropriate and effective system for the treatment of scars, with improvement in scar texture, color, and pliability, with minimal side effects.[25]

5. Cryotherapy

Cryotherapy has been a very effective method to treat small scars, such as severe acne scars.[23] Cryotherapy combined with intralesional Triamcinolone acetonide has been described as the most common traditional therapy for keloids.[26]

6. Radiotherapy

There is a consensus that ionizing irradiation is an effective way to treat keloids.[27] Superficial X-rays, electron-beam therapy and brachy therapy have been used with good results in scar reduction protocols, primarily as adjuncts to surgical removal of keloids.

7. Intralesional corticosteroid injections

Intralesional corticosteroid injections improve scar pliability, diminish its volume and height and reduce scar-related itching and pain.[28] The most used current protocol involves insoluble Triamcinolone acetonide (TAC) (10–40 mg/ml), alone or better in combination with lidocaine, weekly, biweekly or monthly.

8. 5-Fluorouracil (5-FU)

5-FU is a chemotherapy drug, a pyrimidine analog with anti-metabolite activity, effective in the treatment of keloid scars, especially during the first 5 years of appearance.[29] Wound ulceration, hyper pigmentation and pain are potential complications of the treatment. Weekly intralesional 5-FU injections (50 mg/ml) for 12 weeks resulted in reduction of scar size of at least 50% with no recurrence at 24 months.

9. Bleomycin

Bleomycin induces apoptosis, inhibits collagen synthesis via decreased stimulation by TGF-β1, and is frequently used as an antitumor agent.[30]

It has also antibacterial and antiviral activity. Intralesional multiple jet injections of bleomycin 0.1 ml (1.5 IU/ml) at a maximum dose of 6 ml to avoid toxicity (cutaneous and less frequent pulmonary), 2–6 sessions within a month, may currently be indicated as a therapy for keloids unresponsive to intralesional steroid injection, such as patients with old scars; however, its use is still uncommon.[31]

10. Surgery

Surgical treatment of keloids has been usually recommended to be used in mature scars with complementary conservative strategies, such as radiotherapy, bleomycin, cryotherapy or corticosteroids to avoid recurrence (decreasing the risk from 50% to 8% as a combined treatment). Laser and light-based therapies may eliminate the need of classical scar excision and reconstructive surgery in some cases.[5, 28]

Intralesional corticosteroid injections (TAC) And 5-Fluorouracil (5-FU)

Despite relatively few randomized, prospective studies, there is a broad consensus that injected Triamcinolone acetonide is efficacious. It is first-line therapy for the treatment of keloids, if other less invasive treatment have not been efficacious.[32, 33] The main milestone of this treatment is the high frequency of side effects, up to 63%, such as hypo pigmentation, skin atrophy, telangiectasias, rebound effects, ineffectiveness and injection pain.[31]

It has been reported that corticosteroids suppress healing and pathological scarring by three mechanisms: anti-inflammatory and immunosuppressive effect, vasoconstriction, and inhibition of fibroblast and keratinocyte proliferation due to an antimitotic effect.[28]The rates of response to intralesional corticosteroid injections vary from 50% to 100%, with a recurrence rate of 9% to 50%.[34] In this study, we used a dose of 0.1 mL/cm^2 for Triamcinolone acetonide and 0.2 mL/cm^2 for 5-Fluorouracil. These doses were decided based on prior work by Payapvipapong et al. and Kontochristopoulos et al.[35, 36]

5-Fluorouracil is a fluorinated pyrimidine analog that acts as an anti-metabolic agent, inhibiting thymidylate synthase and interfering with RNA synthesis. The rationale for using 5-Fluorouracil stems from a

study conducted by Neil et al., which showed a dose-dependent inhibition of fibroblast proliferation and decrease in collagen synthesis.[12] Through inhibition of these rapidly proliferating cells, scar degradation is stimulated.

Gupta and Kalra conducted a prospective study on 24 consecutive patients with an average of 1.62 keloids per patient. They used a protocol that involved administering 50-150 mg/ml of 5-FU intralesionally on a weekly basis with a maximum of 16 injections per patient. They measured response to treatment by assessing the degree of scar flattening as observed clinically by an observer; at the beginning of the treatment, at the end of the treatment and during follow up. An excellent response to therapy was more than 75% flattening. 33.3% of their patients had excellent flattening and more than 70% had resolution of all accompanying symptoms such as pruritus and pain. Side effects to treatment were limited to pain and mild hyperpigmentation at the injection site. However, no local anaesthetic was used or mixed with the 5-FU solution and the hyperpigmentation eventually disappeared after cessation of treatment. [37]

Nanda and Reddy conducted a similar study that included 28 patients with a varied number of keloids on each patient. They injected 50 mg/ml of 5-FU without lignocaine on a weekly basis for up to 12 weeks, with doses ranging from 0.5ml to 2ml. Assessing outcome was based on patient satisfaction, photographic records and observation by an independent observer. 71% of the patients showed good response to treatment and 7.1% showed excellent response. No treatment failure was recorded. Side effects were limited to pain at the injection site in 100%, ulceration in 21.4% and burning in 7.1%.[38]

A similar study conducted by Kontochristopoulos et al. studied the efficacy of intralesional 5-FU in treating keloids in 20 patients. Eleven of these patients had previous failed therapies. Treatment consisted of injecting between 0.2-0.4ml/cm2 of 50mg/ml 5-FU on a weekly basis. 85% of the patients showed an improvement of more than 50%, determined as scar volume reduction and resolution of symptoms. At

one-year follow up, 9 patients out of 12 (81.8%) with short lasting keloids, defined as less than or equal to two years, showed no signs of recurrence, while in 8 patients with long lasting keloids, defined as more than two years, 6 (66.7%) showed signs of relapse. They concluded that an association exists between duration of keloids and recurrence after treatment with 5-FU.[36]

Prabhu et al. conducted a randomized control trial on 30 patients with keloids and hypertrophic scars. They were randomized into two groups of 15 patients: group A received 50mg/ml of 5-FU with up to 2ml used; group B received 40mg/ml of Triamcinolone acetonide (TAC) with a maximum dose of up to 2ml. The intralesional injections were scheduled on a weekly basis for up to four weeks, with a follow up period of six months, on a monthly basis. Treatment outcome was assessed based on scar volume reduction, which was measured at baseline and later at the end of the treatment using Vernier's calipers. In the 5-FU group, mean reduction in scar volume was 57.21% with a standard deviation of 16.21, while mean reduction in the TAC group was 71.23% with a standard deviation of 18.01. This difference in volume reduction was considerable greater in the TAC group, with a P-value of 0.0402 showing statistical significance. [39]

Saha and Mukhopadhyay conducted a similar randomized controlled trial in order to compare the effect of intralesional 5-FU with intralesional TAC on keloids. 44 patients were randomized into two groups, one receiving intralesional 5-FU and the other intralesional TAC. Injections took place on a weekly basis for a total of 6 weeks. Patients were treated with 50mg/ml of 5-FU and 40mg/ml TAC with a maximum volume injected in both groups, not exceeding 2ml. Reduction in scar volume, presence of itch and pain before and after treatment and side effects of treatment were evaluated. Volume reduction was based on the objective assessment of the same observer taking into consideration flattening, decrease in length and width. All patients in the two groups showed some degree of improvement in terms of volume reduction. 65% of patients in the 5-FU group showed reduction of volume between 51%-100% while 68% of

the TAC group patients showed a similar percentage of volume reduction. Both groups demonstrated resolution of pruritus soon after treatment began. 95% of patients receiving 5-FU experienced pain. Moreover, 65% presented with superficial ulcerations after 2-3 injections. This was not observed in the TAC group.[40] In this study, we injected a maximum dose of 0.6 mL of TAC in a keloid measuring 6 cm^2, and a maximum dose of 2 mL of 5-FU in a keloid measuring 10 $cm^{2.}$.

Ali Sadeghinia et al conducted a study to study 5-FU tattooing and intralesional steroid for treatment of keloids. In this 44-week, double-blind, clinical trial, 40 patients were randomized into two study groups. Patients in group 1 were given intralesional Triamcinolone acetonide (TAC), and patients in group 2 were treated with 5-FU tattooing; both groups received treatment every 4 weeks for 12 weeks. Lesions were assessed for erythema, pruritus, height, surface, and induration at baseline (initiation of treatment) and at weeks 4, 8, 12, 20, 28, 36, and 44. Both groups showed improvement in all parameters, but improvement was more significant in the 5-FU group ($p < 0.05$). No side effect was detected in either of the groups.[3]

Hietanen et al studied efficacy of intralesional 5-Fluorouracil (5-FU) and Triamcinolone acetonide injections in a double-blind randomized controlled trial. Forty-three patients with 50 keloid scars were treated with either intralesional TAC or 5-FU-injections over 6 months. There was no statistically significant difference in the remission rate at 6 months between the 5-FU and TAC groups (46% vs 60%, respectively). Local adverse effects were higher in the TAC group compared to the 5-FU group. Occurrence of skin atrophy in TAC group was 44% and in the 5-FU group 8% ($p < 0.05$). Also, the occurrence of telangiectasia in the TAC group was 50% and in the 5-FU 21% ($p < 0.05$). Vascularity of the keloids, assessed by spectral imaging and immunohistochemical staining for blood vessels, after treatment decreased in the TAC group, but not in the 5-FU group ($p < 0.05$). Fibroblast proliferation evaluated by Ki-67 staining significantly decreased in the TAC group ($p < 0.05$) but increased in the 5-FU group

($p < 0.05$. Due to the greater number of adverse effects observed after TAC treatment, 5-FU injections may be preferable for cosmetically sensitive skin areas.[41]

Sunil Srivastava, et al, conducted a randomized parallel group study in which 60 patients were enrolled and randomly allocated to three groups. Patients received intralesional injections of Triamcinolone acetonide (TAC) in Group TAC, 5-Fluorouracil (5-FU) in Group 5-FU and a combination in Group T+F every 3 weeks till 24 weeks or till the keloid resolved. Reduction in all parameters at every successive assessment in all three groups. Improvement in terms of height, vascularity and pliability was fastest with 5-FU, TAC and T+F group, respectively, which was statistically significant. Decrease in pigmentation was significantly faster with T+F. Reduction in pruritus, however, was significantly faster with 5-FU than the other groups, but the difference in reduction of pain among the three groups was not significant. Telangiectasias and skin atrophy were seen most commonly in TAC group, while skin ulceration was a common problem in 5-FU group.[42]

MATERIALS AND METHODS

Source of Data

All the patients with keloids were treated with intra lesional Triamcinolone acetonide (40 mg/ml) or 5-Fluorouracil (50 mg/ml) at our institution. Total forty patients were enrolled from outpatient clinic.

The patients were divided into two groups, (Group A and Group B) with 20 patients each according to the computer generated randomization list.

Group A patients received intra lesional Triamcinolone acetonide (40 mg/ml) in the dose of 4 mg/cm^2 or 0.1 ml/cm^2 at 3 weeks interval using insulin syringe.

Group B patients received intra lesional 5-Fluorouracil (50 mg/ml) in the dose of 10 mg/cm^2 or 0.2 ml/cm^2 at 3 weeks interval using insulin syringe.

Patients who were part of the study adequately satisfied the inclusion criteria.

METHOD OF COLLECTION OF DATA

INCLUSION CRITERIA

1. Patients with scar size more than 0.5 cm.
2. Patients between the age group of 15 to 60 years.
3. Scars arising after burns, trauma, surgery or infection.

EXCLUSION CRITERIA

1. Patients who had received treatment for the same keloid in the past 6 months.
2. Patients who had infection in or around the keloid.
3. Pregnant females.
4. Patients with chronic inflammatory diseases or those with history of renal or liver failure or immunocompromised patients.
5. Patients with skin allergy or generalized pruritus.

Outcome

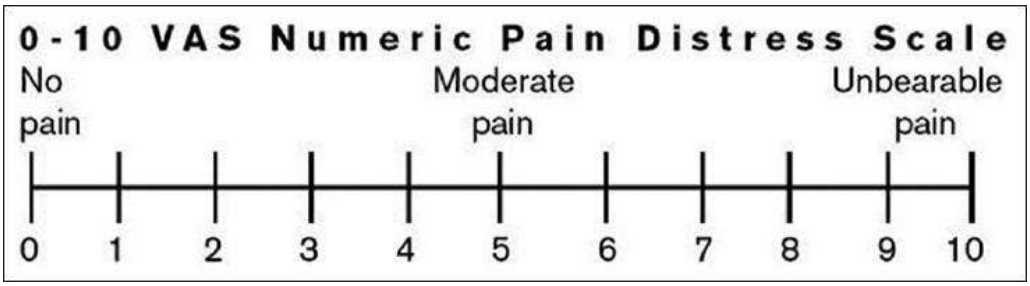
All the patients with keloids were treated with intralesional Triamcinolone acetonide (TAC) or 5-Fluorouracil (5-FU). Assessment of the scar was done using three parameters i.e., Vancouver Scar Scale (to assess change in scar character), Visual Analogue Scale (to assess change/decrease in pain in keloid) and Patient Satisfaction Score (to assess patient satisfaction to treatment). Assessment was done at 3 weekly intervals till the 5^{th} visit or till the scar settled (whichever was earlier). Mean of all the visits was taken for assessing the final outcome.

The Vancouver Scar Scale includes four parameters i.e., Vascularity, Pigmentation, Pliability and Height, with a minimum score of 0 and a maximum score of 13.

Scar characteristic		Score
Vascularity	Normal	0
	Pink	1
	Red	2
	Purple	3
Pigmentation	Normal	0
	Hypopigmentation	1
	Hyperpigmentation	2
Pliability	Normal	0
	Supple (flexible with minimal resistance)	1
	Yielding (giving way to pressure)	2
	Firm (inflexible, not easily moved)	3
	Banding (rope like, blanches with extension of scar, does not limit range of motion)	4
	Contracture (permanent shortening of scar producing deformity, limits range of motion)	5
Height	Flat	0
	$\ll$2 mm	1
	2–5 mm	2
	$\gg$5 mm	3
Total score		13

Vancouver scar scale

Assessment of the pain in keloid scar was done by Visual Analogue Scale (VAS) with range from 0 to 10. This was classified as mild (0-4), moderate (5-7) and severe (8-10) pain.



Visual analogue scale

Patient Satisfaction Score was used for subjectively assessing patient's satisfaction to the intra lesional injections. It ranged from 1 to 3 with 1 as no change/ dissatisfied, 2 as mild change/ equivocal and 3 as significant change/ satisfied.

Any complication such as hypopigmentation, skin atrophy, ulceration and telangiectasia, was noted.

OBSERVATIONS & RESULTS

This study was conducted in the Department of Plastic and Reconstructive Surgery of DMCH, Ludhiana. This study comprised of 40 patients divided into two groups of 20 patients each.

Group A: Patients receiving Triamcinolone acetonide (TAC)

Group B: Patients receiving 5-Fluorouracil (5-FU)

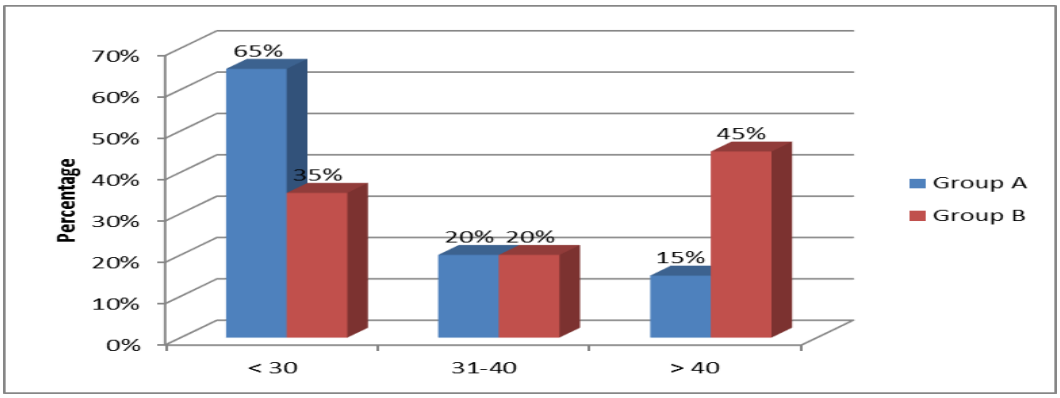
Age

In this study the average age range of the patients was 15 to 59 years.

Table 1: Age

		Group				Total	Chi-square value	p-value
		Group A	Group A	Group B	Group B			
Age	< 30	13	65%	7	35%	20	4.800	0.091
	31-40	4	20%	4	20%	8		
	> 40	3	15%	9	45%	12		
Total		20	100%	20	100%	40		

Figure 1: Age

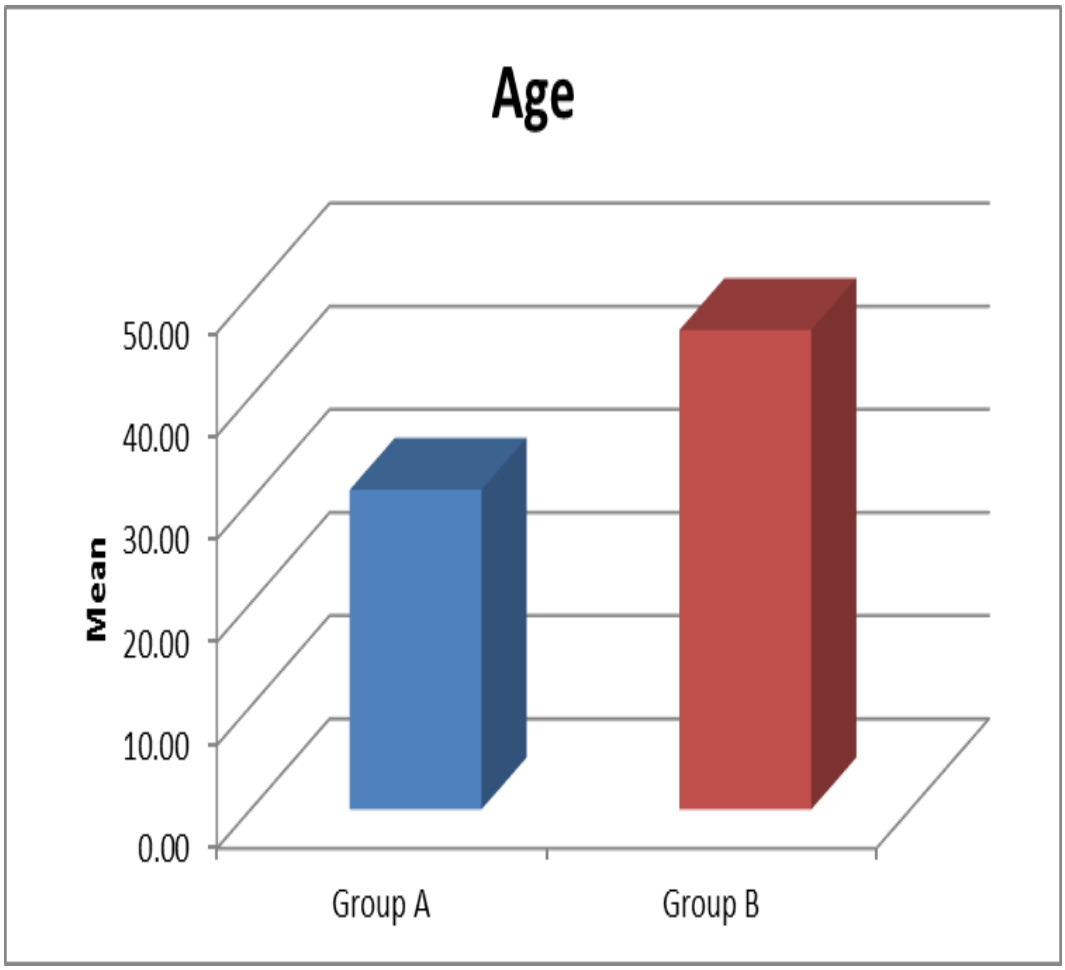


The mean age of the patients in this study was 31.00 years in Group A and was 46.50 years in Group B.

Table 2: Mean Age

	Group A	Group B
Age	31.00	46.50

Figure 2: Mean Age



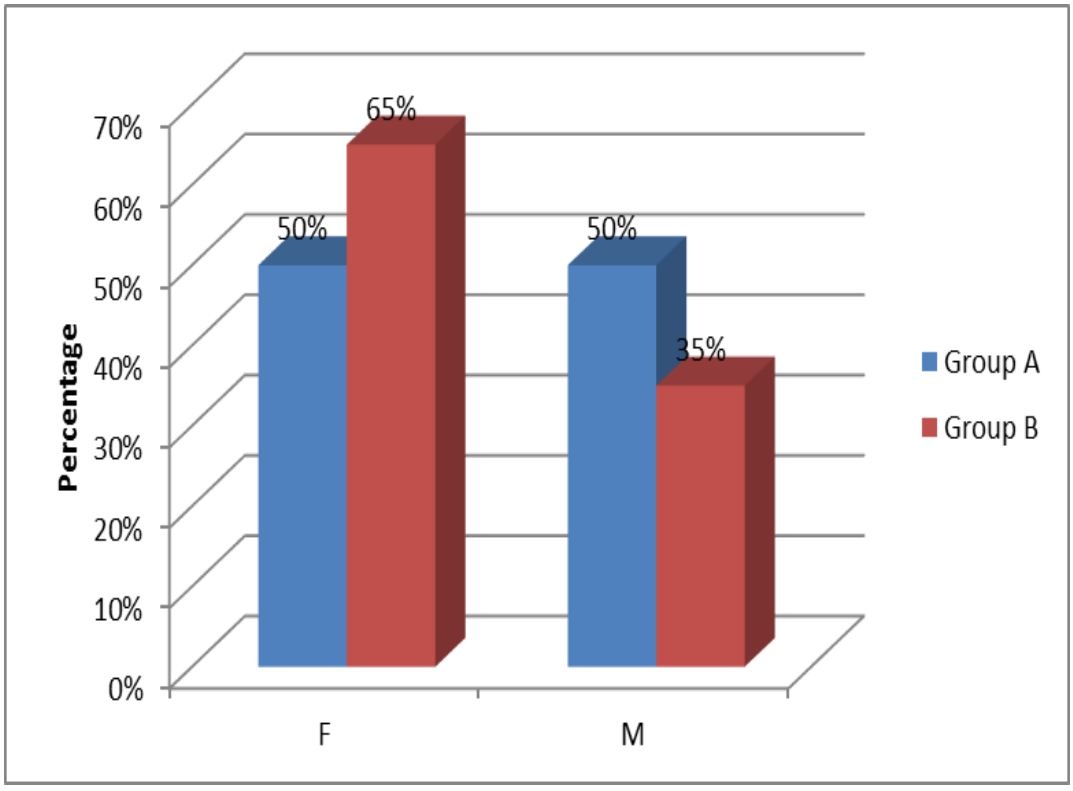
Sex

There were 23 females and 17 males in the study. Group A had 10 females and 10 males, Group B had 13 females and 7 males.

Table 3: Sex

		Group				Total	Chi-square value	p-value
		Group A	Group A	Group B	Group B			
Sex	F	10	50%	13	65%	23	0.921	0.337
	M	10	50%	7	35%	17		
Total		20	100%	20	100%	40		

Figure 3: Sex



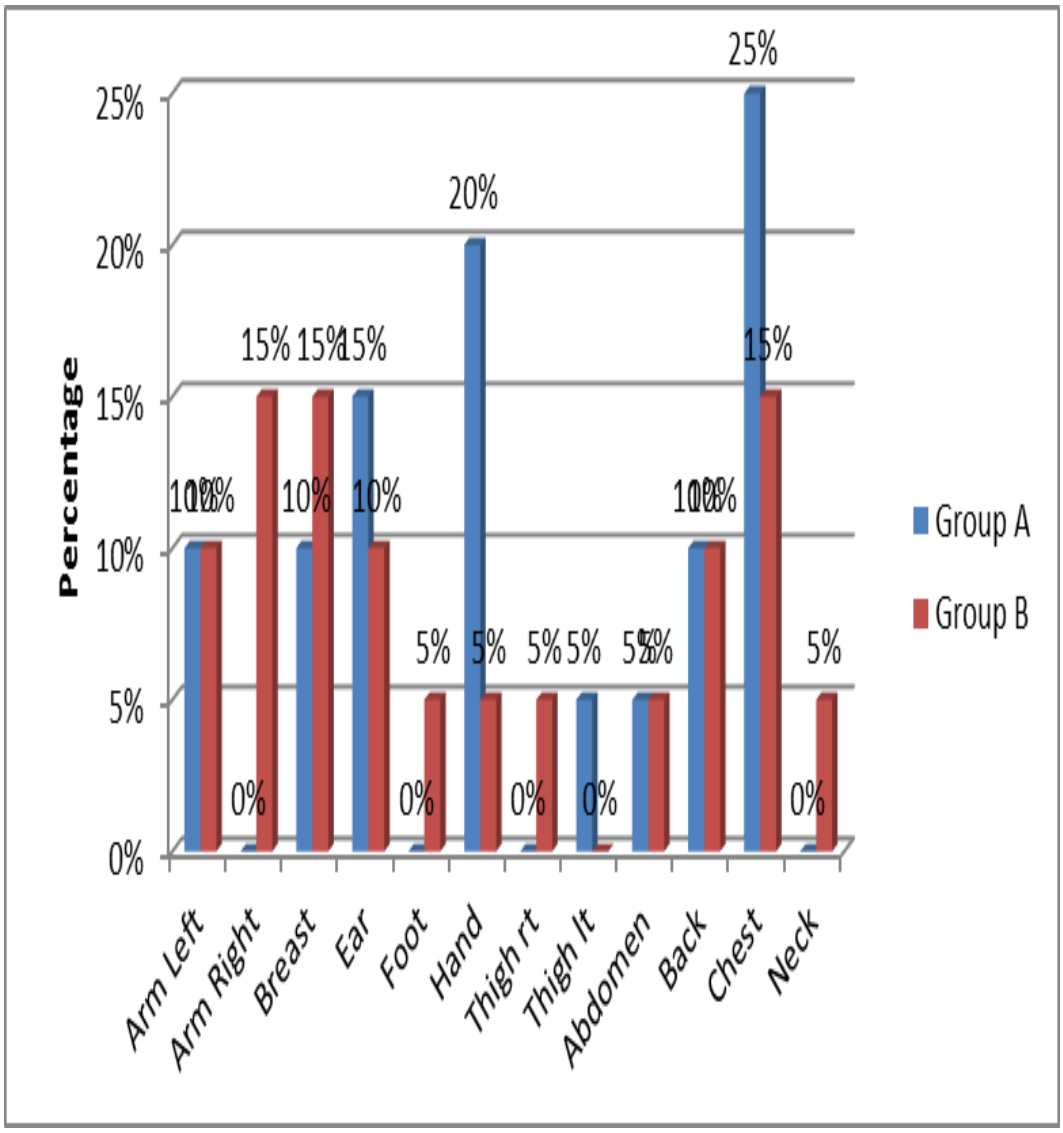
Site of Scar

Chest was the most common site of scar in 8 cases followed by Arm in 7 cases. The other involved sites are shown in Table 4.

Table 4: Site of Scar

		Group				**Total**	**Chi-square value**	**p-value**
		A		**B**				
Site of scar	Arm Left	2	10%	2	10%	4	7.986	0.63
	Arm Right	0	0%	3	15%	3		
	Breast	2	10%	3	15%	5		
	Ear	3	15%	2	10%	5		
	Foot	0	0%	1	5%	1		
	Hand	4	20%	1	5%	5		
	Thigh Right	0	0%	1	5%	1		
	Thigh Left	1	5%	0	0%	1		
	Abdomen	1	5%	1	5%	2		
	Back	2	10%	2	10%	4		
	Chest	5	25%	3	15%	8		
	Neck	0	0%	1	5%	1		
Total		20	100%	20	100%	40		

Figure 4: Site of Scar



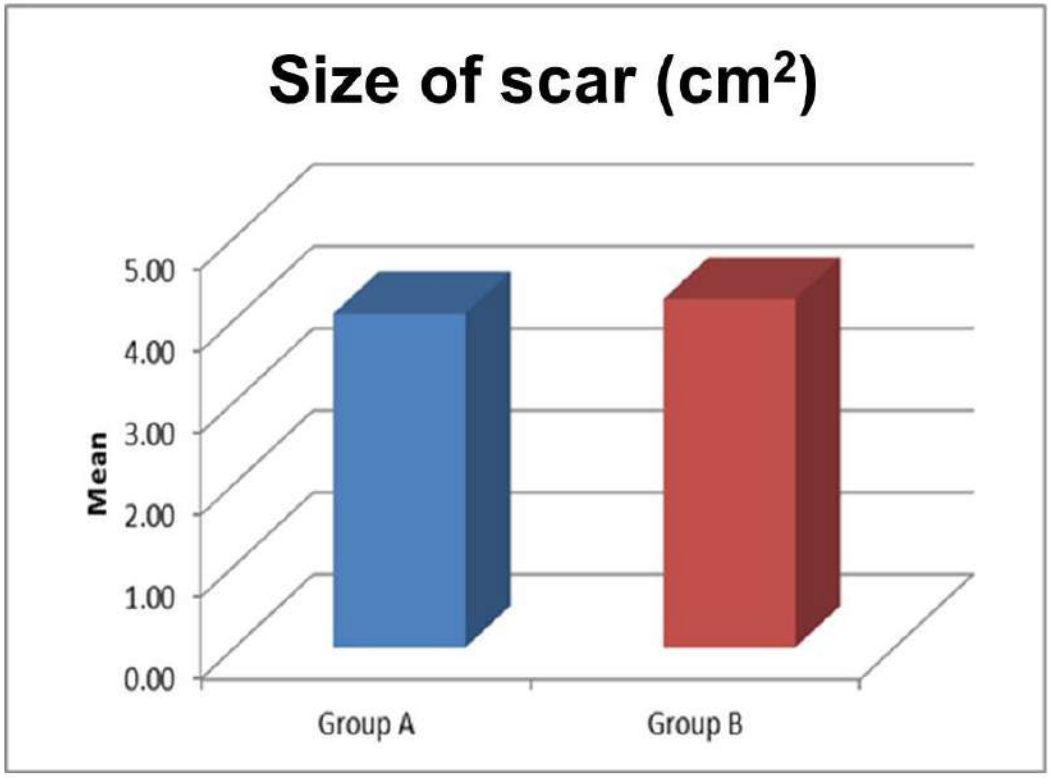
Size of Scar

There was no significant difference in the size of scars between two groups. The average size of the scar was 4.08 cm^2 in group A and 4.25 cm^2 in group B.

Table 5: Size of Scar

	Group A	**Group B**
Size of scar (cm^2)	4.08	4.25

Figure 5: Size of Scar



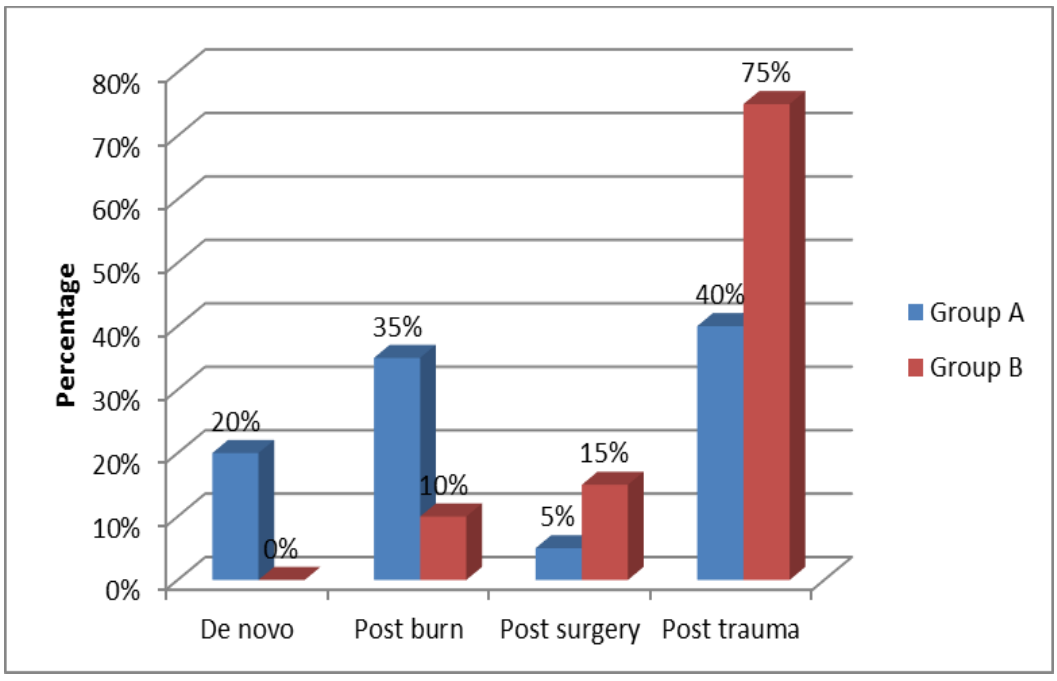
Etiology

Post trauma scarring was the most common etiology with 23 cases (8 cases in Group A and 15 cases in Group B) followed by Post burn scarring in 9 cases (7 cases in Group A and 2 cases in Group B). The other causes included De novo (4 cases in Group A and no case in Group B) and Post surgery keloids (1 case in Group A and 3 cases in Group B).

Table 6: Etiology

		Group				Total	Chi-square value	p-value
		Group A	Group A	Group B	Group B			
Etiology	De novo	4	20%	0	0%	4	9.908	0.019
	Post burn	7	35%	2	10%	9		
	Post surgery	1	5%	3	15%	4		
	Post trauma	8	40%	15	75%	23		
Total		20	100%	20	100%	40		

Figure 6: Etiology



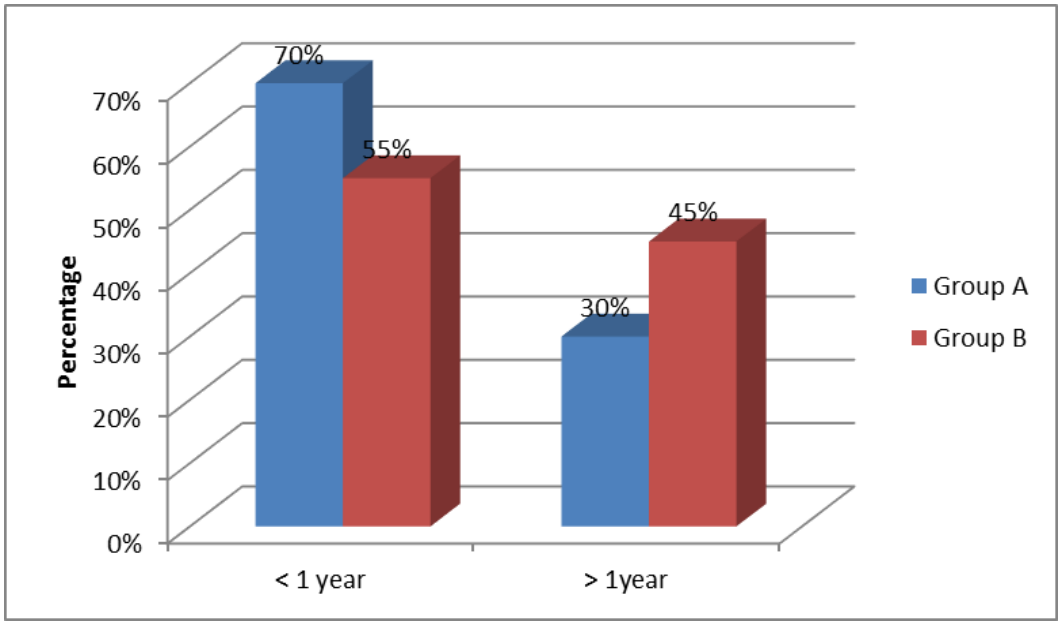
Duration

The duration of presence of the lesion was arbitrarily divided into 2 categories, less than one year and more than one year. In total, 25 cases were of duration less than one year (14 cases in Group A and 11 cases in Group B) and 15 cases were of duration more than one year (6 cases in Group A and 9 cases in Group B).

Table 7: Duration

		Group				Total	Chi-square value	p-value
		Group A	Group A	Group B	Group B			
DURATION	< 1 year	14	70%	11	55%	25	0.96	0.327
	> 1year	6	30%	9	45%	15		
Total		20	100%	20	100%	40		

Figure 7: Duration



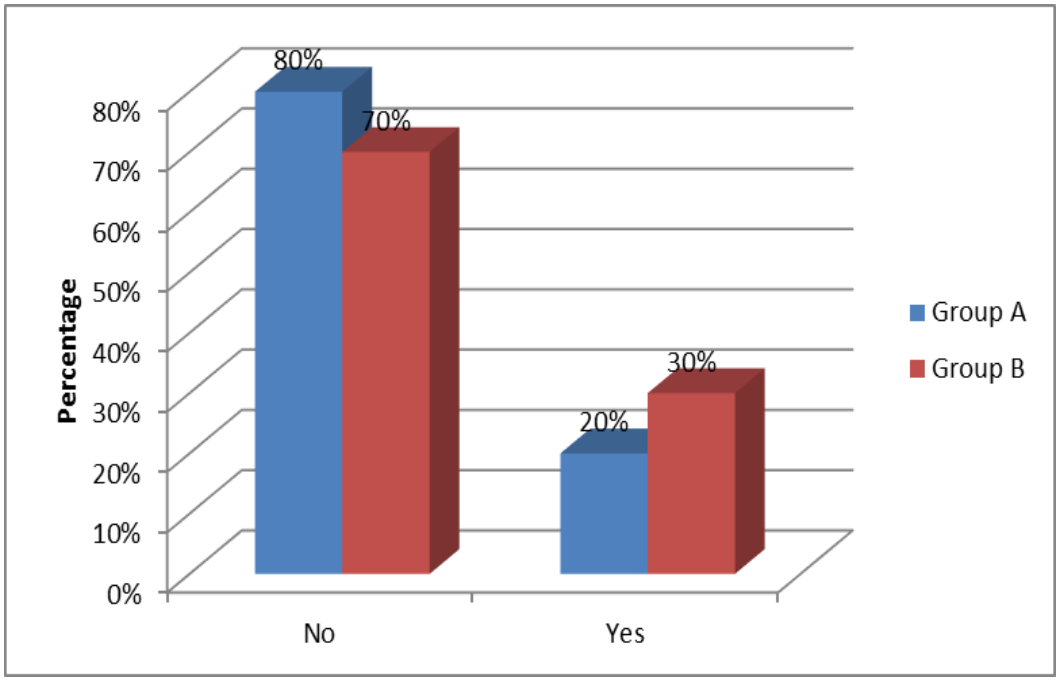
Associated Pruritis

In this study, pruritis was seen in 4 patients (20%) in Group A and 6 patients (30%) in Group B.

Table 8: Associated Pruritis

		Group				Total	Chi-square value	p-value
		Group A	Group A	Group B	Group B			
Associated Pruritis	No	16	80%	14	70%	30	0.533	0.465
	Yes	4	20%	6	30%	10		
Total		20	100%	20	100%	40		

Figure 8: Associated Pruritis



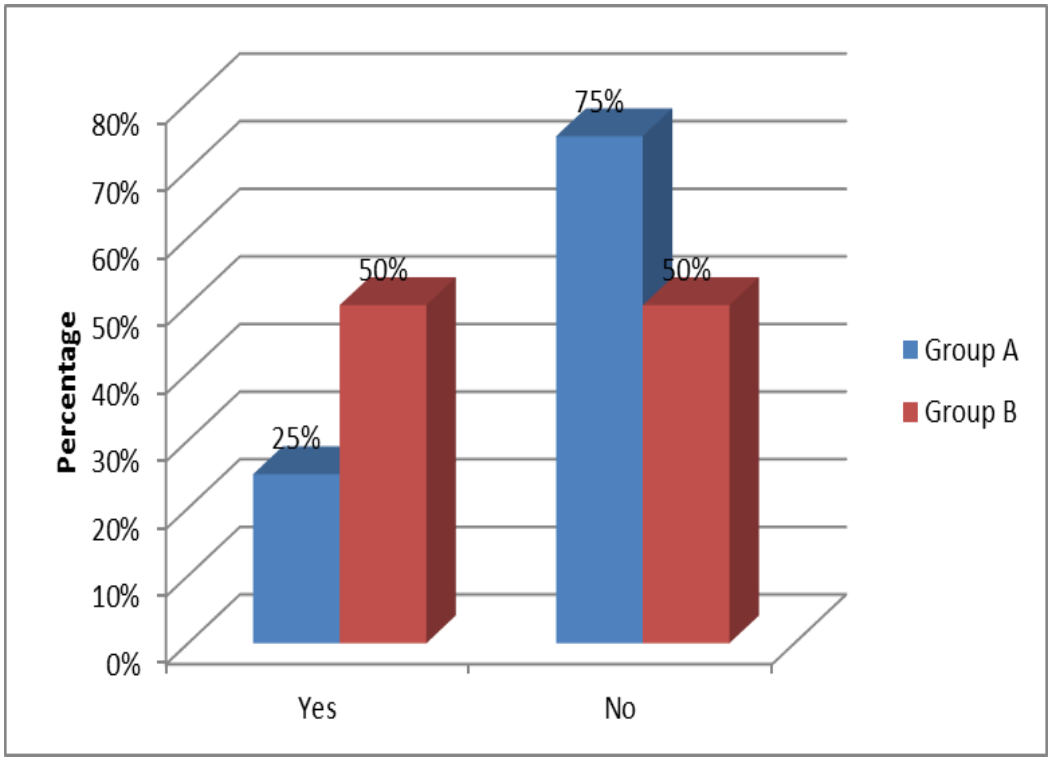
Decrease in Pruritis

In this study, in patients treated with Triamcinolone acetonide (Group A), the decrease in pruritis was seen in only 25% of the patients, (1 out of 4). In patients treated with 5-Fluorouracil (Group B), the decrease in pruritis was seen in 50 % of the patients, (3 out of 6).

Table 9: Decrease in Pruritis

		Group				Total
		Group A	Group A	Group B	Group B	
Decrease in pruritis	Yes	1	25%	3	50%	4
	No	3	75%	3	50%	6
Total		4	100%	6	100%	10

Figure 9: Decrease in Pruritis



Complications

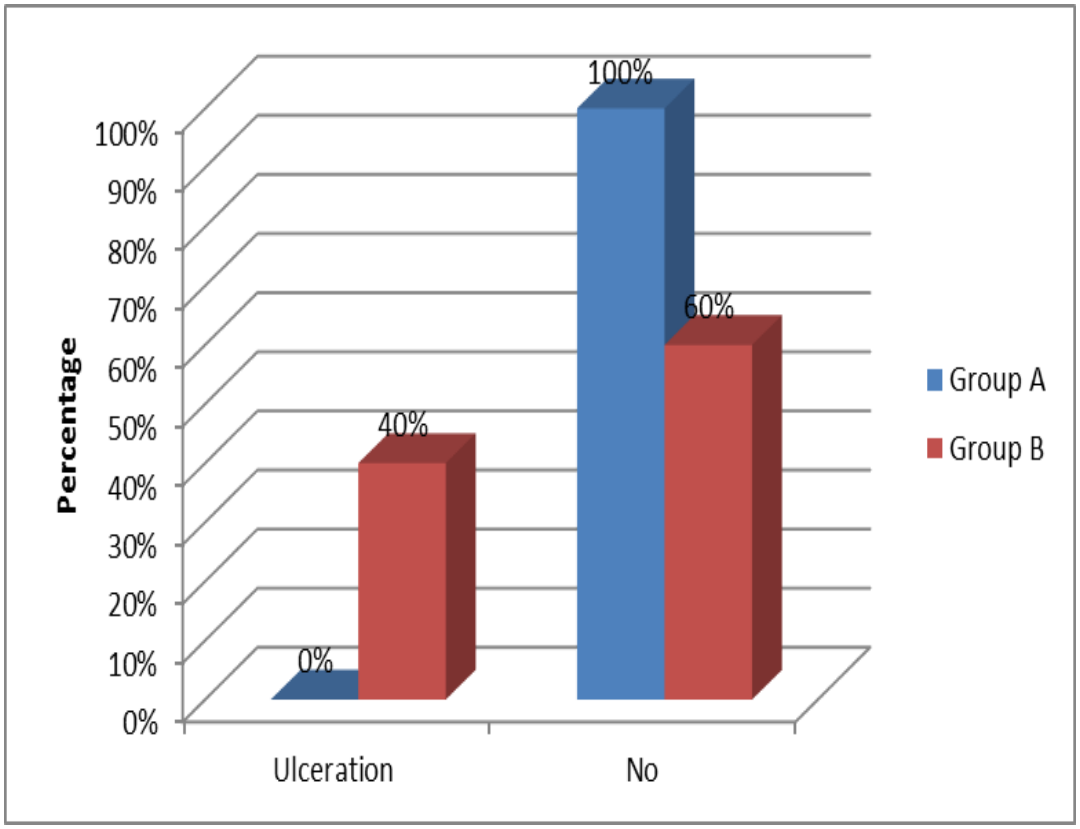
No complication was seen in patient in Group A.

Ulceration was seen as a complication in 8 cases in Group B.

. **Table 10: Complications**

		Group				Total	Chi-square value	p-value
		Group A	Group A	Group B	Group B			
Complications	Ulceration	0	0%	8	40%	8	10	0.003
	Nil	20	100%	12	60%	32		
Total		20	100%	20	100%	40		

Figure 10: Complications

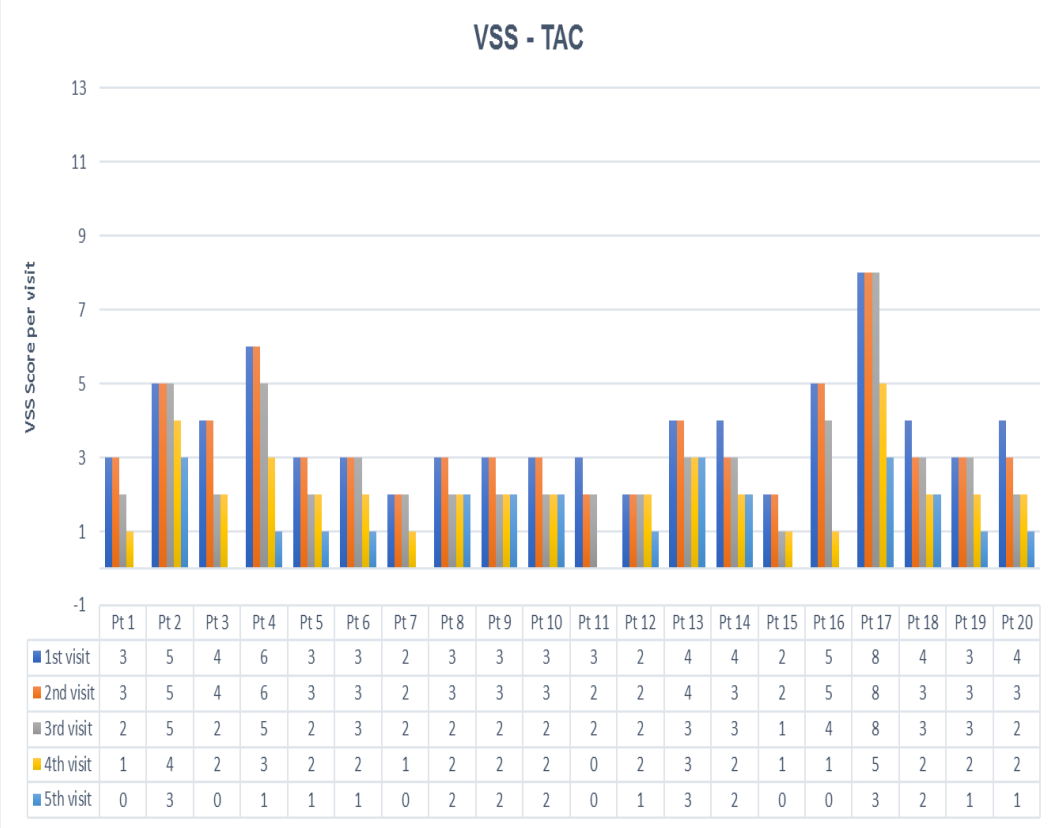


Vancouver Scar Scale

The scar was assessed in terms of pliability, height, pigmentation and vascularity. These parameters were included and a Vancouver scar scale (VSS) was calculated, with a minimum score of 0 and maximum score of 13.

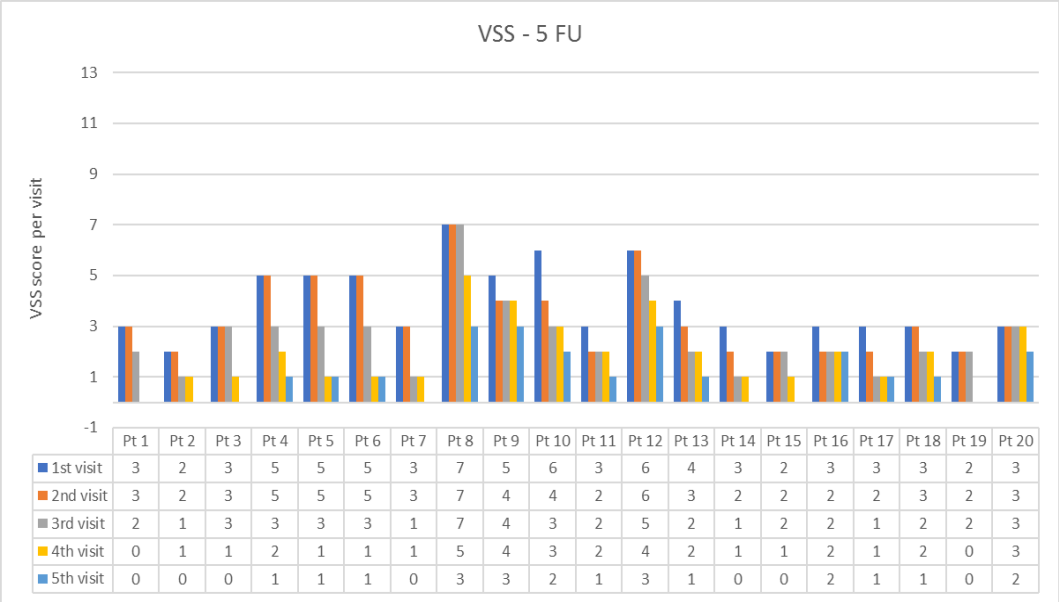
In the TAC group (Group A), 6 patients reported complete regression of keloid, while in the 5-FU group (Group B), 7 patients had complete regression in keloid. A mean VSS was calculated taking into account individual scores from all visits. The mean VSS was reduced in both groups, but was more marked in 5-Fluorouracil (2.57) than Triamcinolone acetonide (2.68). The p-value for mean Vancouver scar scale was 0.769 which was statistically not significant.

Figure 11a: Vancouver Scar Scale - TAC



	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8	Pt 9	Pt 10	Pt 11	Pt 12	Pt 13	Pt 14	Pt 15	Pt 16	Pt 17	Pt 18	Pt 19	Pt 20
1st visit	3	5	4	6	3	3	2	3	3	3	3	2	4	4	2	5	8	4	3	4
2nd visit	3	5	4	6	3	3	2	3	3	3	2	2	4	3	2	5	8	3	3	3
3rd visit	2	5	2	5	2	3	2	2	2	2	2	2	3	3	1	4	8	3	3	2
4th visit	1	4	2	3	2	2	1	2	2	2	0	2	3	2	1	1	5	2	2	2
5th visit	0	3	0	1	1	1	0	2	2	2	0	1	3	2	0	0	3	2	1	1

Figure 11b: Vancouver Scar Scale – 5-FU

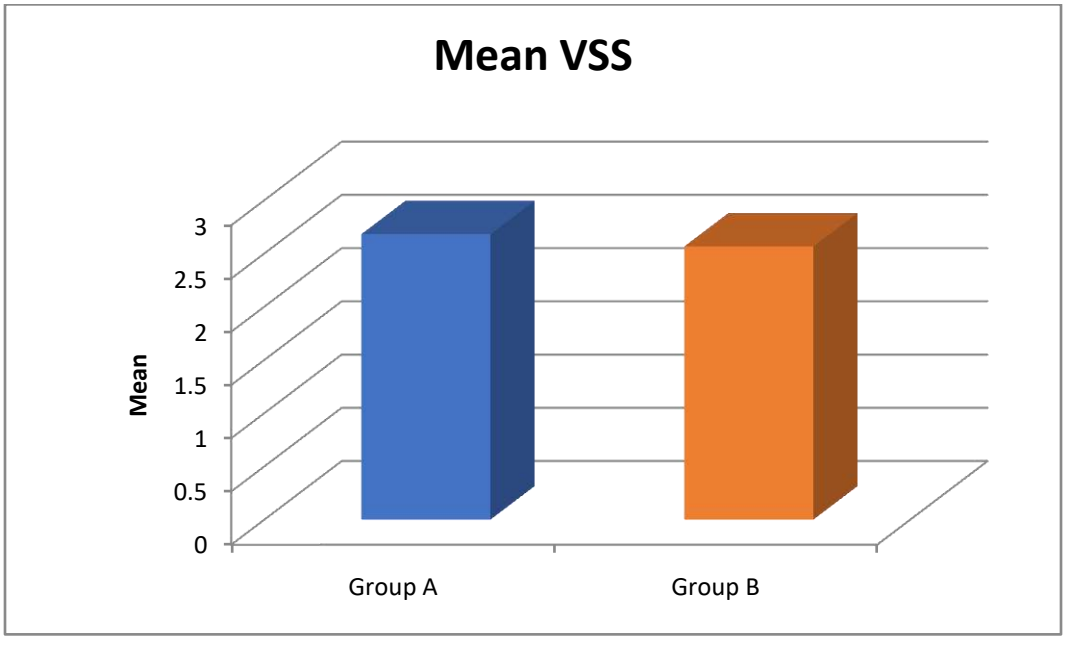


	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8	Pt 9	Pt 10	Pt 11	Pt 12	Pt 13	Pt 14	Pt 15	Pt 16	Pt 17	Pt 18	Pt 19	Pt 20
1st visit	3	2	3	5	5	5	3	7	5	6	3	6	4	3	2	3	3	3	2	3
2nd visit	3	2	3	5	5	5	3	7	4	4	2	6	3	2	2	2	2	3	2	3
3rd visit	2	1	3	3	3	3	1	7	4	3	2	5	2	1	2	2	1	2	2	3
4th visit	0	1	1	2	1	1	1	5	4	3	2	4	2	1	1	2	1	2	0	3
5th visit	0	0	0	1	1	1	0	3	3	2	1	3	1	0	0	2	1	1	0	2

Table 11c Mean Vancouver Scar Scale (VSS)

	Group A		Group B		t	p-value
	Group A	SD	Group B	SD		
Mean VSS	2.68	1.20	2.57	1.26	0.30	0.769

Figure 11c: Mean Vancouver Scar Scale (VSS)



Pain

In this study, in the group receiving Triamcinolone acetonide (Group A), there was only one patient who reported moderate pain (as per VAS score) at the first visit which reduced to mild (as per VAS score) by the next visit. In the group receiving 5-Fluorouracil (Group B), 3 patients reported an increase in pain at the second visit before eventual reduction of pain in the subsequent visits. A mean VAS was calculated taking into account individual scores from all visits. The mean VAS was more marked in 5-Fluorouracil (3.18) than Triamcinolone acetonide (2.085). The p-value for mean Visual analogue scale score was 0.000 which was statistically significant.

Table 12a: VAS score -TAC (Group A)

VAS	1st visit	2nd visit	3rd visit	4th visit	5th visit
Mild	19	20	20	20	20
Moderate	1	0	0	0	0
Severe	0	0	0	0	0

Figure 12a: VAS score -TAC (Group A)

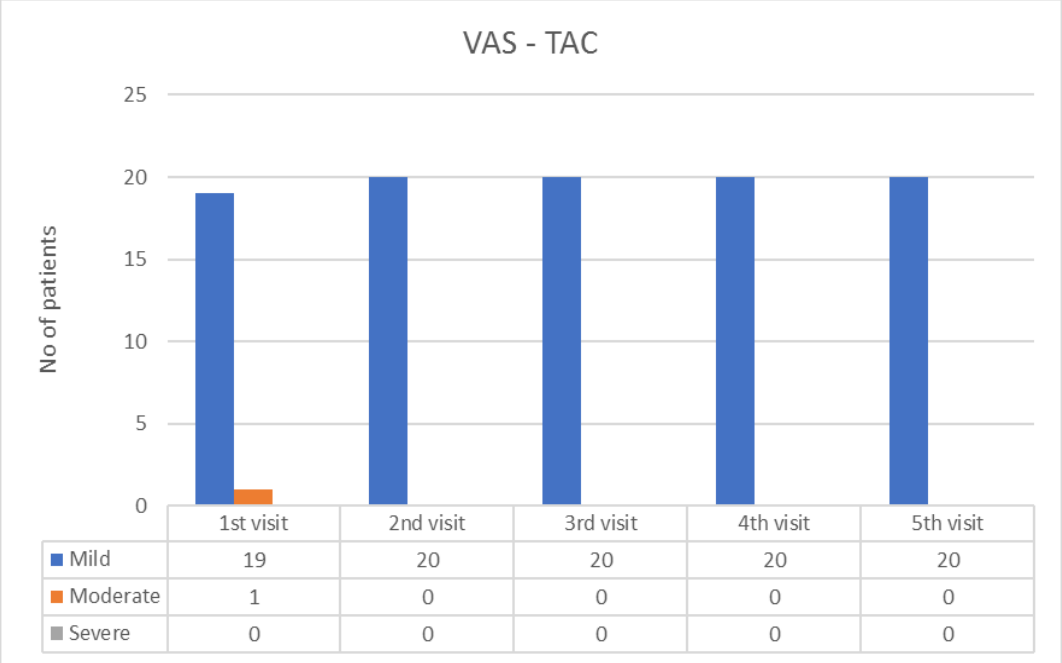


Table 12 (b): VAS score – 5-FU (Group B)

VAS	1st visit	2nd visit	3rd visit	4th visit	5th visit
Mild	19	16	19	20	20
Moderate	1	4	1	0	0
Severe	0	0	0	0	0

Figure 12 (b): VAS score – 5-FU (Group B)

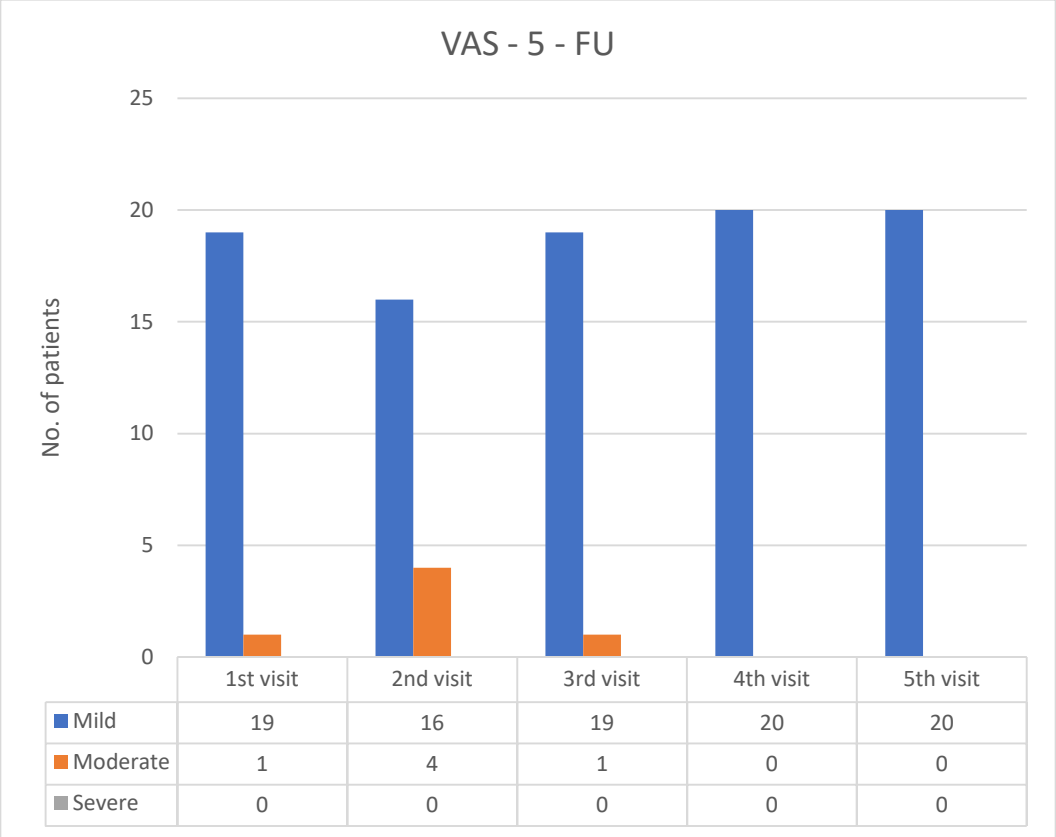
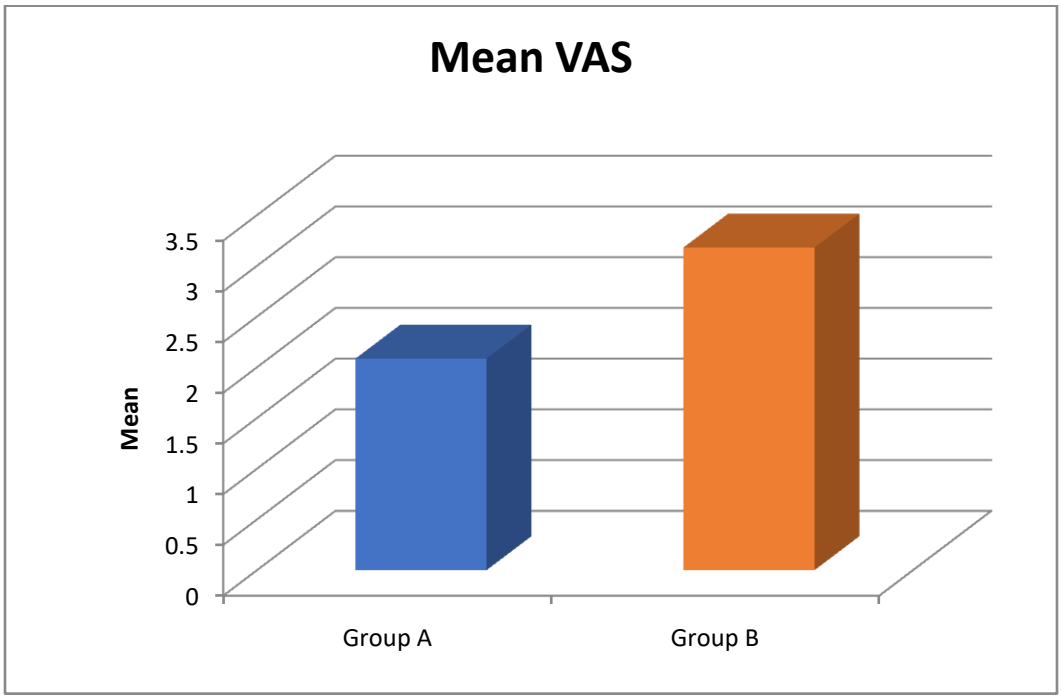


Table 12c: Mean Visual Analogue Score (VAS)

	Group A		Group B		t	p-value
	Group A	SD	Group B	SD		
Mean VAS	2.085	0.61	3.18	0.51	-6.13	0.000

Figure 12c: Mean Visual Analogue Score (VAS)



Patient Satisfaction Score

Patient Satisfaction Score (PSS) was used for subjectively assessing patients' satisfaction to the intra lesional injections. It ranged from 1 to 3 with 1 as no change/ dissatisfied, 2 as mild change/ equivocal and 3 as significant change/ satisfied.

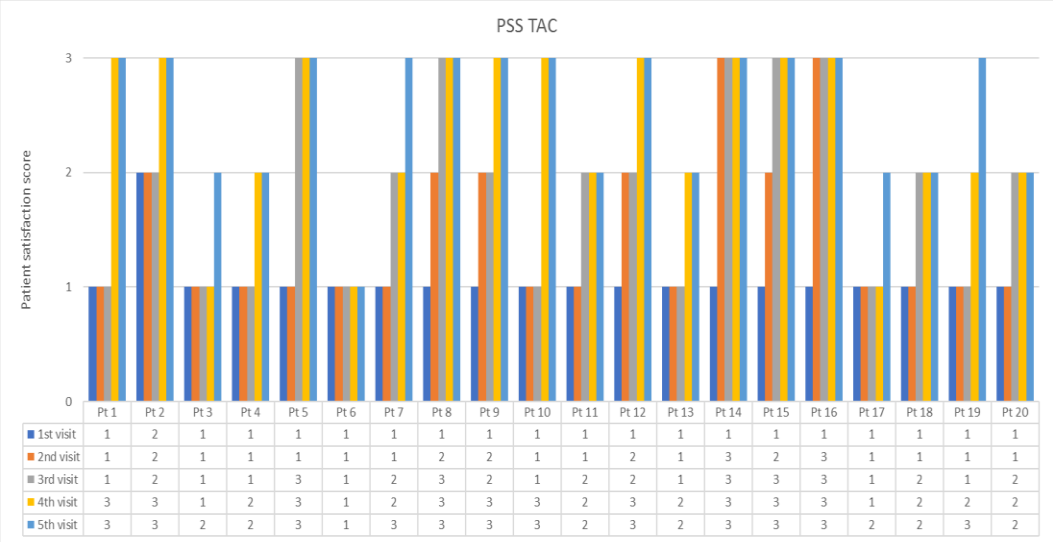
At the end of the 5th visit, in patients who received TAC injections (Group A), 1 patient reported no change, 7 reported mild change and 12 reported significant change.

At the end of the 5th visit, in patients who received 5-FU injections (Group B), 2 patients reported no change, 5 reported mild change and 13 reported significant change. Of note, one patient who had gradual improvement in PSS till the 4th visit in this group, reported sudden dissatisfaction at the 5th visit.

A mean score was calculated for all five visits in both groups.

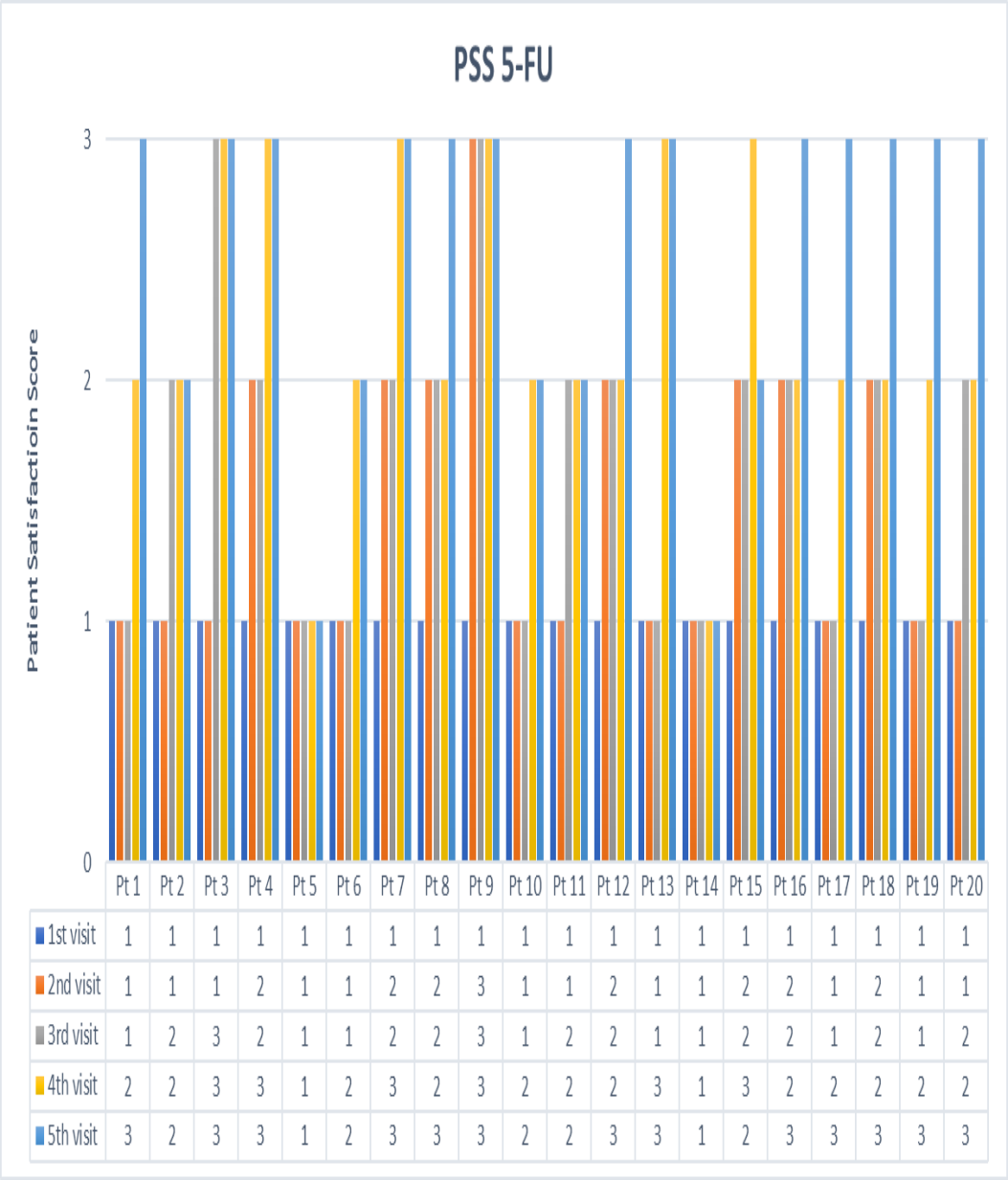
The mean patient satisfaction score was better in Group A (1.97) than Group B (1.78). The p-value for mean Patient Satisfaction Score was 0.203 which was statistically not significant.

Figure 13a: Patient satisfaction score TAC



	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8	Pt 9	Pt 10	Pt 11	Pt 12	Pt 13	Pt 14	Pt 15	Pt 16	Pt 17	Pt 18	Pt 19	Pt 20
1st visit	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2nd visit	1	2	1	1	1	1	1	2	2	1	1	2	1	3	2	3	1	1	1	1
3rd visit	1	2	1	1	3	1	2	3	2	1	2	2	1	3	3	3	1	2	1	2
4th visit	3	3	1	2	3	1	2	3	3	3	2	3	2	3	3	3	1	2	2	2
5th visit	3	3	2	2	3	1	3	3	3	3	2	3	2	3	3	3	2	2	3	2

Figure 13b: Patient satisfaction score 5-FU

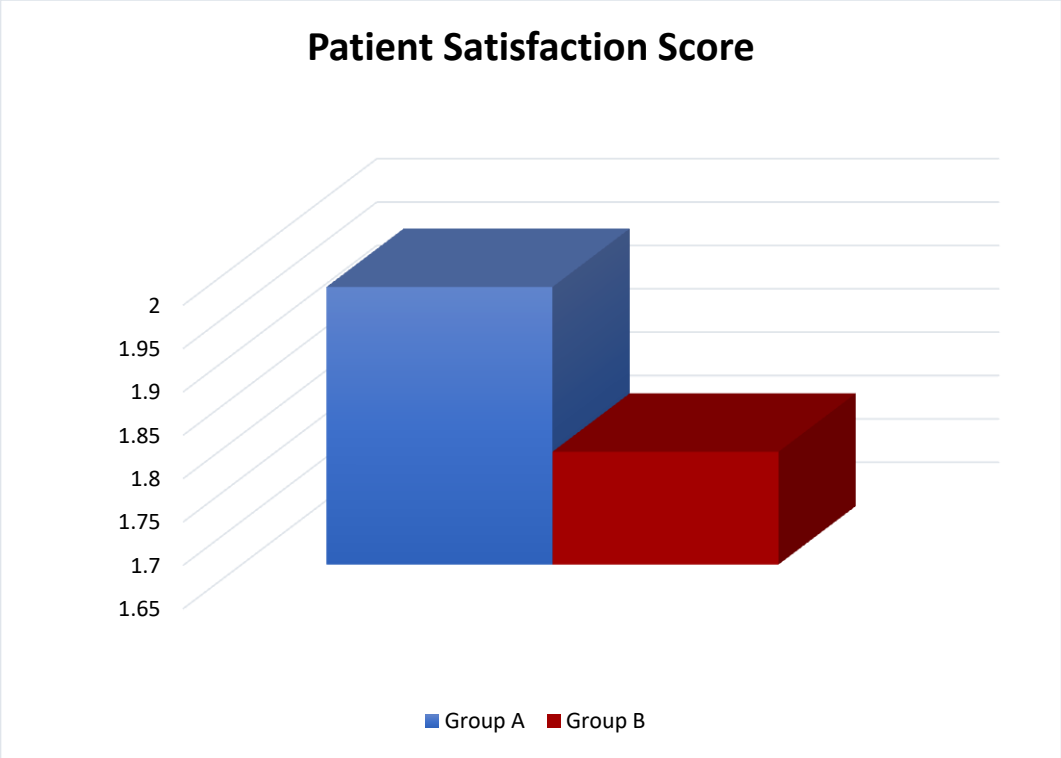


	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8	Pt 9	Pt 10	Pt 11	Pt 12	Pt 13	Pt 14	Pt 15	Pt 16	Pt 17	Pt 18	Pt 19	Pt 20
1st visit	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2nd visit	1	1	1	2	1	1	2	2	3	1	1	2	1	1	2	2	1	2	1	1
3rd visit	1	2	3	2	1	1	2	2	3	1	2	2	1	1	2	2	1	2	1	2
4th visit	2	2	3	3	1	2	3	2	3	2	2	2	3	1	3	2	2	2	2	2
5th visit	3	2	3	3	1	2	3	3	3	2	2	3	3	1	2	3	3	3	3	3

Table 13(c): Mean Patient Satisfaction Score

	Group A		Group B		t	p-value
	Group A	SD	Group B	SD		
Mean Patient Satisfaction Score	1.97	0.52	1.78	0.40	1.30	0.203

Figure13(c): Mean Patient Satisfaction Score



DISCUSSION

Keloids are an unintended consequence of wound healing. Despite the availability of numerous techniques like intralesional agents, massage, manual or mechanical (i.e., compressed air, threadlike shower, etc.), silicone gel, silicone sheets, pressure garments, cryotherapy, radiation therapy and surgery, there is no universally accepted and effective treatment modality.[40]

Owing to the ease of use, availability and efficacy, Intra-lesional agents like Triamcinolone acetonide and 5-Fluorouracil have been used for the management of keloids.[6, 37, 42-45]. The aim of this study was to evaluate and compare the efficacy and acceptability of the two agents for the treatment of keloids and the incidence of complications, if any.

Age

In this study, the age range of the patients is 15 to 59 years which was comparable to a study conducted by Rabello et al. whose study had an average age range of 10 to 30 years.[46]

The mean age of the patients in this study was 36.05 years. The age variable was comparable across both groups, the p value being 0.091.

Although, keloids can occur at any age, they are more commonly seen in younger individuals. It has been suggested that this is due to the fact that the young encounter trauma more frequently and the fact that their skin has greater tension.[20]

Sex

This study had 23 females and 17 males, suggestive of a higher incidence in females. The data in this study was in accordance with the works of Lee et al., Khan et al., Darougheh et al., and Nanda et al. who had a higher proportion of females in their study.[38, 42, 47-49]

Site of lesion

In this study, chest was the most commonly involved site of the lesion (8 patients) comprising 20% of all the patients. The other sites in descending order were the arm, the breast, the ear, the hand and the back. Srivastava

et al., Manzoor et al. and Kontochristopoulos et al. reported chest being the most common site for keloids in their studies.[36, 38, 42, 50, 51] In females, the ear is a common site for keloid formation, but this may be accounted for, due to the higher incidence of ear piercing seen in females.[52]

Size of the lesion

The average size of the keloid was 4.08 cm^2 in TAC group and 4.25 cm^2 in 5-FU group. The two groups were comparable in terms of the size of lesion being studied. To the best of our knowledge, details about the size of the lesion as a comparative parameter have not mentioned in literature.

Etiology

Post traumatic scarring was the most common cause for keloid in 23 cases (57.5 %), followed by post burn scarring in 9 cases (22.5 %). Contrary to this study, Srivastava et al. in their study reported infection to be the most common etiology.[42] In another study by Tandon et al., post traumatic scarring was the most common etiology as seen in over 70% of cases. [51]

Duration

The duration of the presence of the lesion was arbitrarily divided into 2 categories i.e. less than one year and more than one year. The patients with duration of less than one year comprised 25 cases (62.5%), and those with duration of more than one year comprised 15 cases (37.5%). In this study, patients with keloids of duration less than one year responded equally to 5-Fluorouracil as well as Triamcinolone acetonide with a mean VSS on 2.6 in both groups. However, patients with keloid of more than one year duration responded better to TAC (VSS = 2.5), than 5 FU (VSS = 2.8). Gupta et al. reported that keloids present for shorter durations responded better to 5-Fluorouracil in achieving flattening, while Nanda et al. reported no correlation between the duration of the presence of keloid and the therapeutic response obtained.[37, 38]

Pruritis

In this study, itching was present in 10 (30 %) cases. Nanda et al. reported itching to be present in 64.3% of all cases.[38] Kontochristopoulos et al. reported that pruritis was a constant symptom in their study, with softening of the keloid and resolution of pruritis to be the first signs of clinical improvement. Srivastava et al. reported faster reduction in pruritis with 5-Fluorouracil.[42] In this study, 3 out of 6 patients (50%), reported resolution of pruritis after 5-Fluorouracil. In patients treated with Triamcinolone acetonide, this decrease was seen in only 25 % of the patients. (1 out of 4). Davison et al. reported that 93% of all patients receiving 5-Fluorouracil reported resolution of pruritis.[44] Similarly, Sadeghinia et al. too reported that decrease in pruritis was significantly higher with 5-Fluorouracil than Triamcinolone acetonide.[3]

Side effects

Ulceration was seen exclusively in patients who received 5-Fluorouracil, wherein 8 cases (40%) developed this complication. No patient, who received Triamcinolone acetonide has ulceration at keloid site. This finding was similar to the study by Srivastava et al. who reported ulceration in 45% of all cases receiving 5-Fluorouracil, which was not seen in the Triamcinolone acetonide group in their study.[42] Similarly, Kontochristopoulos et al. reported superficial ulcerations in 30% of cases who received 5-Fluorouracil.[36] Tandon et al. too reported ulceration being exclusive to the 5-Fluorouracil in 10% of cases receiving the agent.[51] It has previously been reported that by Manuskiatti et al. that 50% of all lesions receiving steroids experience late side effects like telangiectasia, pigmentation and atrophy. In contrast, patients receiving 5-Fluorouracil experienced no long term side effects.[53] Davison et al. reported a higher incidence of side effects in the 5-Fluorouracil group (23% vs 15%), with telangiectasias being the most common side effect.[44] Mutalik et al. reported that blackish discolouration was the most common side effect seen with intralesional instillation of 5-Fluorouracil.[54] In this study, no

serious long term side effects were noted in either group. Although 5-Fluorouracil can cause anemia, leucopenia and thrombocytopenia this is only seen when the drug is administered systematically. Based on pharmacokinetic studies, 5-Fluorouracil remains in the soft tissue for less than 10 days. Once taken up in the bloodstream, it is degraded within 20 minutes. The metabolites are excreted by the kidney. Drug toxicity is related to intravenous dosing and not with subcutaneous administration.[12, 19]

Effect of agents used

The scar was assessed in terms of pliability, height, pigmentation and vascularity. These parameters were included and a Vancouver scar scale (VSS) was calculated, with a minimum score of 0 and maximum score of 13.

In the TAC group (Group A), 6 patients reported complete regression of keloid, while in the 5-FU group (Group B), 7 patients had complete regression in keloid. A mean VSS was calculated taking into account individual scores from all visits. The mean VSS was reduced in both groups, but was more marked in 5-Fluorouracil (2.57) than Triamcinolone acetonide (2.68).

Srivastava et al. also noted that improvement in the VSS was markedly faster with 5-Fluorouracil when compared to Triamcinolone acetonide.[42] Tandon et al. however noted that reduction in VSS score was markedly more in the Triamcinolone acetonide group than the 5-Fluorouracil group.[51] Heitanen et al. reported that treatment efficacy of 5-Fluorouracil and Triamcinolone acetonide was same. However, they noted that the vascularity of the keloids decreased in the Triamcinolone acetonide group, but not in the 5-Fluorouracil group.[41] Sadeghinia et al. reported a significantly greater decrease in height and surface of keloids when treated with 5-Fluorouracil as compared to Triamcinolone acetonide.[3] No such selective discernable effects on height or surface area were observed with either agent in this study. Manuskiatti et al. reported that

significant softening of the lesion was faster with Triamcinolone acetonide (as early as 8 weeks), than 5-Fluorouracil (at 18 weeks). However, they also noted that scar erythema did not respond to Triamcinolone acetonide, but responded to 5-Fluorouracil.[53] It was observed, in this study, that reduction in pliability of keloid was faster with TAC (earliest at second visit) than 5-FU (earliest at fourth visit). Manzoor et al. reported that a pre-determined level of response to treatment was achieved faster with 5-Fluorouracil, than Triamcinolone acetonide.[50] In this study, a positive response to treatment was seen in both groups, but the response was markedly greater in the 5-Fluorouracil group. The p-value for mean Vancouver scar scale was 0.769, which was statistically not significant.

Pain

Though pain was not a significant presenting symptom still we subjectively assessed pain following treatment with intralesional TAC and 5-FU. In this study, pain was evaluated using the Visual Analogue Scale (VAS). The pain was assessed before initiating the treatment and subsequently at each visit. In this study, in the group receiving Triamcinolone acetonide (Group A), there was only one patient who reported moderate pain (as per VAS score) which reduced to mild (as per VAS score) by the next visit. In the group receiving 5-Fluorouracil (Group B), 3 patients reported an increase in pain at the second visit before eventual reduction in pain in the subsequent visits. A mean VAS was calculated taking into account individual scores from all visits. The mean VAS was more marked in 5-Fluorouracil (3.18) than Triamcinolone acetonide (2.085). The p-value for mean Visual analogue scale score was 0.000, which was statistically significant.

Patient satisfaction score

Patient Satisfaction Score (PSS) was used for subjectively assessing patients' satisfaction to the intra lesional injections. It ranged from 1 to 3 with 1 as no change/ dissatisfied, 2 as mild change/ equivocal and 3 as significant change/ satisfied.

At the end of the 5th visit, in patients who received TAC injections (Group A), 1 patient reported no change, 7 reported mild change and 12 reported significant change.

At the end of the 5th visit, in patients who received 5-FU injections (Group B), 2 patients reported no change, 5 reported mild change and 13 reported significant change. Of note, one patient who had gradual improvement in PSS till the 4th visit in this group, reported sudden dissatisfaction at the 5th visit.

A mean score was calculated for all five visits in both groups.

The mean patient satisfaction score was better in Group A (1.97) than Group B (1.78). The p-value for mean Patient Satisfaction Score was 0.203, which was statistically not significant.

In a study, conducted by Sadeghinia et al. patient satisfaction was better with 5-Fluorouracil when compared to Triamcinolone acetonide, on a 5 point subjective scale.[3] Manuskiatti et al. noted that patient satisfaction was equal with both 5-Fluorouracil and Triamcinolone acetonide as graded by patients as being completely clear(100% improvement) or placed in catagories of 25% increments compared with a standard pre treatment photograph.[53]

CONCLUSIONS

Triamcinolone acetonide and 5–Fluorouracil are two commonly used agents for the treatment of keloids.

This comparative study was conducted at Dayanand Medical College and Hospital to compare the efficacy of Triamcinolone acetonide and 5-Fluorouracil in treatment of keloids.

We concluded that –

1. 5-Fluorouracil elicits a better response than Triamcinolone acetonide in terms of pliability, height, pigmentation and vascularity of keloid scars.
2. 5-Fluorouracil results in better resolution of keloids.
3. 5-Fluorouracil is less well tolerated and is associated with more side effects especially ulceration at injection site.
4. Patient satisfaction score is better with Triamcinolone acetonide though the keloid resolution and pain reduction are better with 5-Fluorouracil.

Although our study provides evidence for efficacy of both agents, the study was limited by small sample size and short follow up.

Further studies and meta analysis are required to provide a definitive answer.

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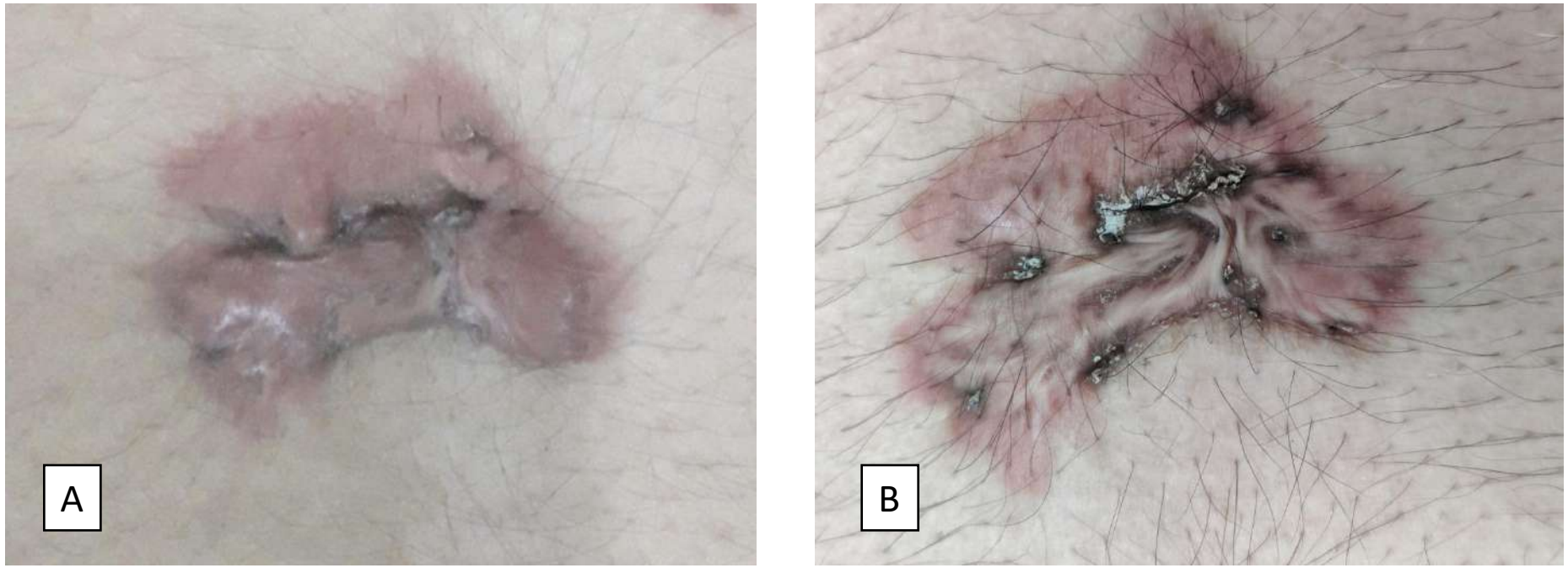
Picture 1. Injection 5 – Fluorouracil (left), insulin syringe (center) and Injection Triamcinolone acetonide (right)

Picture 2. Keloid over sternum with telangiectasia

Picture 3. Keloid over shoulder

Picture 4. Arm keloid treated with TAC: (A) At first visit, (B) At third visit and (C) At fifth visit



Picture 5. Sternal Keloid treated with 5-FU:
(A) At first visit, (B) At fifth visit

Picture 6. Shoulder Keloid treated with 5-FU: (A) At first visit, (B) At second visit with visible ulceration of surface and (C) At fifth visit

PROFORMA

Case no.

Name Age/Sex

Address

Duration of scar:

Etiology of scar:

Site of scar:

Size of scar:

Associated Pruritis:

Any complications:

Scar Assessment

A. VANCOUVER SCAR SCALE(VSS):

1. Vascularity

Normal(0)

Red(1)

Pink(2)

Purple(3)

2. Pigmentation

Normal(0)

Hypopigmented(1)

Mixed(2)

Hyperpigmented(3)

3. Pliability

Normal(0)

Signature of Candidate **Signature of Supervisor**

Supple(1)

Yielding(2)

Firm(3)

Rope like(4)

Contracture(5)

4. Height

Flat(0)

<2mm(1)

2-5mm(2)

>5mm(3)

B. VISUAL ANALOGUE SCALE(VAS) FOR PAIN(1-10):

C.PATIENT SATISFACTION SCORE(1-3):

1-NO CHANGE

2-MILD CHANGE

3-SIGNIFICANT CHANGE

Signature of Candidate **Signature of Supervisor**

S. No	Randomized No. (Group A and Group B)	Name	Age/Sex	Site of scar	Size of scar (cm^2)	Etiology	Duration	Associated Pruritis	Decrease in Pruritis	Complications	Mean VSS	Mean VAS	Mean Patient Satisfaction Score
1	B	S	52/F	Left hand	1.5 cm	Post trauma	2 months	No	-	No	1.2	3.4	1.6
2	B	KS	30/M	Neck	4 cm	Post trauma	1 months	No	-	No	1.6	3.2	1.6
3	B	P	28/F	Left arm	5 cm	Post trauma	4 months	No	-	No	2	3	2.2
4	A	AK	26/F	Right Wrist	5 cm	Post surgery	4 months	No	-	No	2.4	2.2	1.8
5	B	AS	28/M	Right elbow	6 cm	Post burn	2 months	No	-	Ulceration	4	2.8	2.2
6	A	JS	26/M	Right Ear	1.5 cm	Post trauma	2 months	No	-	No	1.2	2.6	2.4
7	A	AK	25/M	Left Arm	5 cm	Post burn	3 months	No	-	No	4.4	1.8	1.2
8	B	AS	28/M	Right forearm	10 cm	Post burn	2 months	No	-	Ulceration	5.8	3	1
9	A	JK	45/F	Right Thigh	3 cm	Post trauma	2 months	No	-	No	1.8	2.2	1.4
10	A	AK	25/M	Left hand	4 cm	Post burn	3 months	No	-	No	6.4	2	2.2
11	B	S	52/F	Right Breast	6 cm	Post trauma	5 years	Yes	Yes	No	1.6	4.4	1.4
12	A	S	52/F	Upper chest	4 cm	Post trauma	10 years	Yes	Yes	No	4.2	1.8	1
13	B	DK	50/M	Upper Chest	3 cm	Post surgery	2 years	No	-	Ulceration	3	3.2	2.2
14	A	AS	28/M	Right thumb	3 cm	Post burn	2 months	No	-	No	2.2	3	1.8
15	B	DK	50/M	Chest	2.5 cm	Post surgery	2 years	No	-	Ulceration	3	3	2
16	B	DK	50/M	Sternum	2.5 cm	Post surgery	2 years	No	-	Ulceration	3.5	1.8	2.6
17	A	NK	23/F	Right ear	2 cm	Post trauma	1.5 years	No	-	No	2.8	1.6	2.4
18	A	KS	27/M	Left hand	6 cm	Post trauma	9 months	No	-	No	3	2.6	2.2
19	A	R	20/F	Chest	4 cm	De novo	5 months	No	-	No	2.4	1.8	1.8
20	A	JK	25/F	Breast	6cm	Post burn	8 months	No	-	No	2.4	2.6	1.6
21	A	PS	30/M	Chest	4 cm	De novo	5 months	No	-	No	2.8	2.8	2.2
22	B	A	25/F	Right ear	1 cm	Post trauma	3 monts	No	-	No	1.2	3.2	1.4
23	A	BS	40M	Chest	3 cm	Post trauma	7 months	No	-	No	1.4	1.5	1.4
24	B	R	39/F	Right Breast	1.5 cm	Post trauma	6 months	No	-	No	1.4	2.4	1.6
25	A	HK	23/F	Left arm	3 cm	Post trauma	5 months	No	-	No	2.4	2.6	2.6
26	A	A	34/F	Left ear	2 cm	Post trauma	4 months	No	-	No	2.4	2.8	2.4
27	B	R	39/F	Left thigh	3 cm	Post trauma	6 months	No	-	No	2	3.4	2
28	A	SK	27/F	Right Breast	5 cm	Post burn	5 months	No	-	No	1.4	0.4	2.6
29	B	R	39/F	Right foot	2 cm	Post trauma	6 months	No	-	Ulceration	2.2	3.6	1.8
30	B	P	15/M	Chest	6 cm	Post trauma	1 year	No	-	No	2.8	3.2	1
31	B	NK	23/F	Left ear	6 cm	Post trauma	4 months	No	-	No	4.8	3.4	2
32	B	NK	59/F	Abdomen	10 cm	Post trauma	5 years	Yes	Yes	Ulceration	3.6	3.8	2
33	B	NK	59/F	Back	3 cm	Post trauma	5 years	Yes	Yes	No	1.6	3.2	1.6
34	A	TS	40/M	Abdomen	6 cm	Post burn	3 years	No	-	No	2.4	2	1.2
35	B	GK	38/F	Back	2 cm	Post trauma	6 months	Yes	No	No	2.4	3.4	2
36	B	NK	59/F	Left arm	3 cm	Post trauma	5 years	Yes	No	No	1.4	3	1.6
37	A	R	27/F	Back	4 cm	De novo	8 years	Yes	No	No	1.8	1.6	2.4
38	A	S	32/M	Chest	5 cm	Post burn	1 year	Yes	No	No	3.4	2.2	2.4
39	A	KS	45/M	Back	6 cm	De novo	4 years	Yes	No	No	2.4	1.6	2.4
40	B	NK	59/F	Right arm	7 cm	Post trauma	5 years	Yes	No	Ulceration	2.2	3.2	1.8

COMPARATIVE EFFICACY OF INTRA LESIONAL TRIAMCINOLONE ACETONIDE AND 5-FLUOROURACIL FOR KELOIDS

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

MCh IN

PLASTIC SURGERY

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES

FARIDKOT

APRIL, 2019

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DEPARTMENT OF PLASTIC & RECONSTRUCTIVE SURGERY
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ABSTRACT OF PLAN OF THESIS

Title	COMPARATIVE EFFICACY OF INTRA LESIONAL TRIAMCINOLONE ACETONIDE AND 5-FLUOROURACIL FOR KELOIDS
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Introduction: A keloid is an overgrowth of dense and fibrous tissue usually developing after healing of skin injury. There are various non surgical and surgical modalities for the treatment of the keloids. Intra lesional triamcinolone and 5-Fluorouracil are the most commonly used these days for the keloids. In this study we will compare the efficacy of these two drugs in the treatment of keloids.

Aim of Study: Comparative analysis of the efficacy of intra lesional triamcinolone and 5-Fluorouracil for keloids.

Materials and Methods: All the patients with keloids will be treated with intra lesional triamcinolone(TAC) or 5-Fluorouracil(FU) at our institution. Total 40 patients will be enrolled from outpatient clinic. The patients will be divided into two groups as Group A and Group B with 20 patients each.

Group A patients will receive intra lesional triamcinolone(40mg/ml) at 3 weeks interval using insulin syringe mixed with injection lignocaine in 1:1 ratio.

Group B patients will receive intra lesional 5-FU(50mg/ml) at 3 weeks interval using insulin syringe mixed with injection lignocaine in the ratio of 1:1.

Clinical Significance: All the patients with the keloids will be treated with intralesional triamcinolone or 5-FU. Assessment of the scar will be done by Vancouver scar scale, Visual Analogue Scale(VAS) for pain and patient satisfaction score at every visit. Follow up will be done till 5th visit in all cases.

Keywords: Keloids, Intra lesional, Triamcinolone, 5-Fluorouracil.

(Signature)	(Signature)	(Signature)	(Signature)	(Signature)
Candidate	Co-supervisor	Co-supervisor	Supervisor	Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"COMPARATIVE EFFICACY OF INTRA LESIONAL TRIAMCINOLONE ACETONIDE AND 5-FLUOROURACIL FOR KELOIDS"** exist in the Department of plastic & reconstructive surgery, DMCH Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis are genuine and is collected by the candidate himself/herself under our supervision and guidance.

Supervisor

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Research Committee

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Approved: Yes / ~~No~~

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BABA FARID UNIVERSITY OF HEALTH SCIENCES, FARIDKOT

PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

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4	DATE OF ADMISSION OF COURSE	23-AUG-2018
5	TITLE OF THE TOPIC	COMPARATIVE EFFICACY OF INTRALESIONAL TRIAMCINOLONE ACETONIDE AND 5-FLUOROURACIL FOR KELOIDS.

6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

A keloid is an overgrowth of dense and fibrous tissue usually developing after healing of skin injury. This tissue extends beyond the borders of the original wound, does not regress spontaneously and tends to recur after excision. Keloids appear as firm, mildly tender, bosselated tumours with a shiny surface and occasional telengiectasia. They continue to evolve over time and do infilterate the surrounding tissue.[1]

There is a lack of consensus about an ideal standard therapy, so there is a significant need for an effective treatment protocol because keloids are common and tend to reoccur.[2]

Keloids could be managed by non surgical and surgical methods.

Non surgical measures include the use of application of silicon gel with or without pressure therapy, intralesional drugs injection, laser therapy, cryotherapy, radiation, surgery etc.

Newer modalities include imiquimod 5% cream, Intra lesional Botulinum toxin A, Interferon-alfa2b, photodynamic therapy and Recombinant TGF-beta3 (Avotermin).

Intra lesional drugs could be steroid (Triamcinolone) or chemotherapeutic agents like 5-Fluorouracil and Bleomycin.

Among all these, intra lesional tiamcinolone and 5-Fluorouracil are most commonly used agents.

Intralesional steroid injections have been used for the therapy of excessive scar since the mid-1960.[3]

Effect of corticosteroids result primarily from their suppressive effects on the inflammatory process in the wound and secondarily from the reduced collagen and glycosaminoglycan synthesis, inhibition of fibroblast growth, as well as enhanced collagen and fibroblast degeneration.[4-6]

In addition the side effects of intralesional steroid injection are common. Telengiectasias, hypopigmentation and skin atrophy have been reported.[7]

The interest in anti neoplastic agents like 5-Fluorouracil and Bleomycin as a therapeutic modality is logical, because keloids have been shown to exist in a hypermetabolic state.[8]

5-Fluorouracil has a comparatively faster response in scar flattening. Both in vitro and in vivo studies have confirmed that 5-Fluorouracil inhibits collagen synthesis.[8-12]

5-Fluorouracil inhibits the proliferation of fibroblasts as a pyrimidine analog. The response rate in keloids is an estimated 50%.

Intralesional triamcinolone and 5-Fluorouracil are proven therapies for the management of keloids but the comparative efficacy of these two have not been studied much.

Further, there is paucity of studies determining the interval at which intralesional triamcinolone and 5- Fluorouracil should be administered in the management of keloids, the hypothesis is that three and four weekly interval is the best interval in terms of maximum results and least complications.

In this study we will compare the efficacy of the Intralesional triamcinolone and 5-Fluorouracil for keloids by Vancouver Scar Scale, Visual analogue scale(for pain) and Patient Satisfaction Score.

6.2 REVIEW OF LITERATURE

.Asboe - Hansen found that with the long standing edema the mucopolysacchride content in the skin is maintained at a high level and this stimulates the deposition of the collagen fibres and thus keloid formation.[13]

Multiple studies on hypertrophic scar or keloid formation have led to a multitude of therapeutic strategies to prevent or improve keloid formation and have been reviewed in a plethora of articles.

Intralesional steroid injections have been used for the therapy of excessive scars since the mid-1960s. To date, the use of intralesional triamcinolone acetonide represents the therapy of choice for small and younger keloids and effectively provides symptomatic relief by reducing pruritus. It has been reported that steroid suppress healing and pathological scarring by anti inflammatory effect, vasoconstriction and inhibition of fibroblast and keratinocyte proliferation due to an anti mitotic effect.[14]

The rates of response to intra lesional corticosteroid injections vary from 50% to 100% with a recurrence rate of 9% to 50%.[14]

Three to four injections of triamcinolone acetonide (TAC) (10–40 mg/mL) every 3–4 weeks are generally sufficient, although occasionally injections continue for 6 months or more. The rates of response to intralesional corticosteroid injections vary from 50% to 100% with a recurrence rate of 9% to 50%.[14]

A study conducted bt Perdanasari et al (2014) reviewed the latest literature available on the subject of intra lesional therapy for keloid management and summarized the mechanism of each treatment, its benefits and associated adverse effects and possible strategies to address adverse reactions. They

observed that depending on the size and site of the lesion and on the age of the patient, the dosage has varied from 10 to 40 mg/ml and treatment is administered at intervals of 4 to 6 weeks for several months or until the scar flattened. The corticoid should be injected at the correct depth in the mid dermis to avoid irreversible atrophy of the epidermis. Injections should be repeared once every 3-4 weeks depending on the bulk of the keloid and the therapeutic response.[15]

Nanda and Reddy studied the effects of 5-Fluorouracil in 28 patients with keloids on the chest, shoulder, upper arms, back, and additional locations. Eight patients had previously failed to respond to triamcinolone acetonide (TAC) 40 mg/cc injections every 3 weeks. Weekly intralesional injections of 0.5–2 ml of 50 mg/ml 5-Fluorouracil per session were administered for no more than 12 weeks. There was good improvement in 71.4% patients and excellent improvement in 7.1% patients. Follow-up at 24 weeks revealed no recurrences. Adverse effects included pain in 100%, ulceration in 21.4%, and burning in 7.1% of patients.[16]

Kontochristopoulus et al. also investigated the effects of intralesional 5-Fluorouracil in 20 patients with keloid lesions. Eleven patients had previously failed treatment with steroid injections, silicone gels, surgical excision, and cryotherapy. Weekly intralesional injections of 0.2–0.4 ml/cm^2 of 50 mg/ml 5-Fluorouracil were administered over an average of seven sessions. Forty percent of patients had good improvement, and 5% had excellent improvement. At 52-week follow-up, 47% demonstrated reoccurrence. All patients experienced pain and transient hyperpigmentation, and six patients had superficial ulceration.[17]

In a study by Srivasta, 60 patients were enrolled and randomly allocated to three groups. Patients received intralesional injections of triamcinolone acetonide (TAC) in Group TAC, 5-fluorouracil (5FU) in Group 5FU, and a combination in Group T + F every 3 weeks till 24 weeks or till the keloid resolved.. Significant differences among groups in terms of reduction of vascularity and pliability were noted after the sixth week, while that of height and pigmentation were noted after the third week.[18]

Adverse sequelae like hypo or depigmentation, telangiectasia and atrophy are seen in about 20% of the cases injected with triamcinolone.

5-Fluorouracil a pyrimidine analogue, was first introduced in the treatment of keloid by Fitzpatrick who published his results in 1999.[19] 5 FU inhibits fibroblast proliferation. It also has an inhibitory effect on TGF-Beta induced expression of the type 1 collagen gene. 5-Flourouracil has a comparatively faster response in scar flattening. Combining TAC with 5- FU has been suggested to have a rapid response in terms of scar flattening with an added advantage of fewer side effects.

The interest in antineoplastic agents as a therapeutic modality is logical, because keloids have been shown to exist in a hypermetabolic state. Both in vitro and in vivo studies have confirmed that 5- Flourouracil inhibits collagen synthesis.

There are a number of clinical reports in the literature regarding the efficacy of various anti neoplastic drugs on modification of scarring.

In 2006, Liu et al and Wu et al promoted a "low-dose" therapy using 1.4–3.5 mg/mL 5-Fluorouracil in 35 patients with 51 keloids. In 2008 and 2009, the

same group could demonstrate the effectiveness of this therapy in 83 patients with a total of 166 keloids on the ear.[20-22]

In another double-blind, prospective study on 40 patients with keloids and hypertrophic scars, better results with respect to reduction in size and redness were seen with the combination TAC (40 mg/mL)/5-Fluorouracil (50 mg/mL) (1:9) compared with the injection of TAC 40 mg/mL alone.[23]

6.3 AIMS AND OBJECTIVES

Comparative efficacy of intralesional Triamcenolone and 5-Fluorouracil for keloids.

7.0 MATERIALS AND METHODS

7.1 Source of Data

All the patients with keloids will be treated with intra lesional triamcinonlone (40mg/ml) or 5-Fluorouracil(50mg/ml) at our institution. Total 40 patients will be enrolled from outpatient clinic.

The patients will be divided into two groups as Group A and Group B with 20 patients each.

Group A patients will receive intra lesional triamcinolone (40mg/ml) in the dose of $4mg/cm^2$ or $0.1ml/cm^2$ at 3 weeks interval using insulin syringe mixed with injection lignocaine in the ration of 1:1 to reduce pain during injection.

Group B patients will receive intra lesional 5-Fluorouracil (50mg/ml) in the dose of $10mg/cm^2$ or $0.2ml/cm^2$ at 3 weeks interval using insulin syringe mixed with injection lignocaine in 1:1 ratio to decrease pain during injection.

Those who are the part of study will have to satisfy the inclusion criteria. For randomization, computer generated list is used.

7.2 METHOD OF COLLECTION OF DATA

INCLUSION CRITERIA

1. Patients with scar size more than 0.5 cm.
2. Patients between the age group of 15 to 60 years.
3. Scars arising after burns, trauma, surgery or infection.

EXCLUSION CRITERIA

1. Patients who had received treatment for the same keloid in the past 6 months.
2. Patients who have infection in or around the keloid.
3. Pregnant females.

4. Patients with chronic inflammatory diseases or those with the history of renal or liver failure or immunosuppressed patients
5. Patients with skin allergy or generalized pruritis

Outcome

All the patients with the keloids will be treated with intralesional triamcinolone(TAC) or Fluorouracil(FU). Assessment of the scar will be done using three parameters i.e. Vancouver Scar Scale, Visual Analogue Scale and Patient Satisfaction Score. Assessment will be done 3 weekly intervals till the 5^{th} visit or till the scar settles (whichever is earlier). Mean of all the visits will be taken for assessing the final outcome.

Vancouver Scar Scale includes four parameters i.e. Vascularity, Pigmentation, Pliability and Height.

Assessment of the pain will be done by Visual Analogue Scale(VAS) which ranges from 1-10 with1-no pain and 10-worst pain.

Patient Satisfaction Score will be used for subjectively assessing patient's satisfaction to the intra lesional injections. It will range from 1 to 3 with 1 as no change, 2 as mild change and 3 as significant change.

Any complication such as hypopigmentation, skin atrophy, telengiectasias will be noted.

STATISTICAL ANALYSIS

Data will be described in terms of range; mean ±standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. Comparison of quantitative variables between the study groups will be done using Student t-test and Mann Whitney U test for independent samples for parametric and non-parametric data respectively.

For comparing categorical data, Chi square ($\chi 2$) test will be performed and exact test was used when the expected frequency is less than 5. A probability value (p value) less than 0.05 will be considered statistically significant. All statistical calculations will be done using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Windows.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY

Yes, the Investigations considered necessary by the treating doctors/department will be evaluated. The investigations are:

Routine investigations– HEMOGRAM, BT,CT, RFT,LFT

7.4 HAS ETHICAL CLEARENCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Attached herewith.

8.0 LIST OF REFERENCES

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PROFORMA

Case no.

Name Age/Sex

Address

Duration of scar:

Etiology of scar:

Site of scar:

Size of scar:

Associated Pruritis:

Any complications:

Scar Assessment

A. VANCOUVER SCAR SCALE(VSS):

1. Vascularity

Normal(0)

Red(1)

Pink(2)

Purple(3)

2. Pigmentation

Normal(0)

Hypopigmented(1)

Mixed(2)

Hyperpigmented(3)

3. Pliability

Normal(0)

Signature of Candidate

Signature of Supervisor

Supple(1)

Yielding(2)

Firm(3)

Rope like(4)

Contracture(5)

4. Height

Flat(0)

<2mm(1)

2-5mm(2)

>5mm(3)

B. VISUAL ANALOGUE SCALE(VAS) FOR PAIN(1-10):

C.PATIENT SATISFACTION SCORE(1-3):

1-NO CHANGE

2-MILD CHANGE

3-SIGNIFICANT CHANGE

Signature of Candidate

Signature of Supervisor

CERTIFICATE OF DEPARTMENTAL CLEARANCE

This is to certify that the plan of thesis entitled **"COMPARATIVE EFFICACY OF INTRA LESIONAL TRIAMCINOLONE ACETONIDE AND 5-FLUOROURACIL FOR KELOIDS"** has been discussed in the Department of Plastic & Reconstructive Surgery, Dayanand Medical College and Hospital, Ludhiana and approved by whole of the faculty of the Department. The plan writing is satisfactory.

Supervisor

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Associate Professor
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Head of the Department

Dr Sanjeev K Uppal
Professor& Head
Department of Plastic surgery
DMCH, Ludhiana

DAYANAND MEDICAL COLLEGE & HOSPITAL
LUDHIANA

Ref. No: DMCH/

Dated:

TO WHOM IT MAY CONCERN

Certified that the study entitled "**COMPARATIVE EFFICACY OF INTRA LESIONAL TRIAMCINOLONE ACETONIDE AND 5-FLUOROURACIL FOR KELOIDS"** involves only such investigations and / or treatment, which are relevant in the management of patients and has no extra cost implications to the patient.

Name of candidate:	Dr Amandeep
Supervisor:	Dr Ramneesh Garg
Co-Supervisor(s):	Dr. Sanjeev Uppal
	Dr Rajinder K Mittal

Signature of candidate

Signature of Supervisor

DAYANAND MEDICAL COLLEGE & HOSPITAL, LUDHIANA

Ref. No. DMCH/ Dated:

TO WHOM IT MAY CONCERN

I shall carry out the study **"COMPARATIVE EFFICACY OF INTRA LESIONAL TRIAMCINOLONE ACETONIDE AND 5-FLUOROURACIL FOR KELOIDS"** meticulously and shall maintain the records for 5 years after the submission of thesis and present them to any competent authority as and when required. The following documents will be preserved:

1. List of enrolled patients with identification details
2. Consent forms of all the enrolled patients
3. Proforma of each patient with verifiable details, individually signed by supervisor.

Dr. Amandeep
MCh Resident
Dept. of Plastic & Reconstructive Surgery
DMC & Hospital, Ludhiana

CERTIFICATE

We hereby certify that the informed patient consent form and its translation and back translation to Hindi and Punjabi are accurate to the best of our knowledge and satisfaction.

Supervisor

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DMCH, Ludhiana

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Dr. Amandeep
MCh Resident
Dept. of Plastic & Reconstructive Surgery
DMC & Hospital, Ludhiana

INFORMED PATIENT CONSENT

Date: _____

I.....D/o, W/o, S/o.....

am willing to participate in the study "**COMPARATIVE EFFICACY OF INTRA LESIONAL TRIAMCINOLONE ACETONIDE AND 5-FLUOROURACIL FOR KELOIDS"** The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

.....
Signature of the Witness

Name:

.....
Signature of the patient

Signature of Candidate

Signature of Supervisor

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य **"COMPARATIVE EFFICACY OF INTRA LESIONAL TRIAMCINOLONE ACETONIDE AND 5-FLUOROURACIL FOR KELOIDS"** में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____

गवाह के हस्ताक्षर

नाम:

_____

रोगी के हस्ताक्षर/अंगूठे का निशान

नाम:

_____

अन्वेषक के हस्ताक्षर

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

"COMPARATIVE EFFICACY OF INTRA LESIONAL TRIAMCINOLONE ACETONIDE AND 5-FLUOROURACIL FOR KELOIDS" ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

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ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____ ਮਿਤੀ_____

ਪਤਾ _____ ਪਤਾ _____

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ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

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ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ